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The Problem of Complete Y-Linkage in Man[1]

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THE FIRST CHROMOSOME IN MAN which was identified as the carrier of specific genes was the X chromosome (Wilson 1911). The second and, at present, the only other identifiable chromosome for which such a status has been claimed is the Y chromosome.

Inheritance through the Y chromosome, Y-linkage, may occur in two ways, complete and incomplete. In complete Y-linkage a gene responsible for a certain trait is solely confined to a locus in the Y chromosome either because it has no allele in the X chromosome or because it does not exchange with an X chromosomal allele. In incomplete Y-linkage, or more correctly, incomplete sex linkage, there are homologous loci in the X and Y chromosomes whose alleles cross over from one sex chromosome to the other. In organisms with heterogamy of the male sex, complete Y-linkage of genes with full penetrance leads to the following phenomena:

a) The trait occurs in males only.

b) It reoccurs in all sons of affected males.

c) The daughters of affected men are not only phenotypically normal but also do not have affected offspring.

Incompletely sex linked genes behave differently from completely X- or Y-linked genes. In complete X-linkage a gene is located in a portion of the X chromosome which does not undergo exchanges with the Y chromosome. Such genes follow the classical distribution of the X chromosomes. In particular, a heterogametic XY parent transmits his X-linked genes exclusively to his XX offspring. Conversely, in complete Y-linkage, the XY parent gives his Y-linked genes exclusively to his XY offspring. In incomplete sex-linkage both XX and XY offspring may inherit a specific allele of the gene concerned, in frequencies which depend on the amount of crossing over between the homologous regions of the X and Y chromosomes.

It was not until 1920 that the Y chromosome in any species was shown to be concerned with the transmission of a particular gene. In that year Johannes Schmidt demonstrated the role of the Y chromosome in the genetics of a pigment spot in the fish *Lebistes reticulatus*, a discovery which, in 1921, was also reported by Aida for color inheritance in the fish, *Aplocheilus latipes*. In the following years, a few more cases of Y-linked inheritance became known; further examples in *Lebistes* (Winge 1922a, b)[2]; a color trait in the beetle *Phytodecta variabilis* (Zulueta 1925); bristle size in *Drosophila*

[1] The material of this paper formed the basis for the Presidential Address "On porcupine skin and hairy ears; or, The alleged sins of the Y chromosome" delivered at the tenth annual meeting of the American Society of Human Genetics at the University of Michigan, Ann Arbor, Michigan, April 13, 1957.

[2] For references to later works on Lebistes by various authors, see Winge and Ditlevsen 1938.

(Stern 1926, 1927); and the only Y-linkages in plants, concerned with general morphological abnormality and with chlorophyll variegation respectively, in *Melandrium album* and *M. rubrum* (Winge 1931). In *Drosophila*, the Y chromosome is also known to influence the degree of position effect variegation (Gowen and Gay, 1933, 1934) and to cause variegation of eye color if present in double dose in normal females, or triple dose in normal males (Cooper 1956). Other examples of special morphological expressions of the Y chromosome in *Drosophila* have been given by L. V. Morgan (1947), and Goldschmidt, Hannah, and Piternick (1951). Action of Y chromosomes on quantitative characters of *Drosophila* has been reported by Mather (1944), Barrigozzi (1948), and Barrigozzi and di Pasquale (1953). For a review of much of the work on the Y chromosome of *Drosophila* and additional literature see Hannah (1951).

The Y chromosome is concerned with sex determination in the fishes mentioned above, the gypsy moth *Lymantria dispar* (see Goldschmidt 1934), the silk worm *Bombyx mori* (Tazima 1943, 1944 quoted from Goldschmidt 1955), the mosquito *Culex molestus* (Gilchrist and Haldane 1947), several species of the midge *Chironomus* (Beerman 1955) and the plant *Melandrium* (Warmke and Blakeslee 1939, Warmke 1946, Ono 1940 a and b, Westergaard 1940, 1948).

In *Drosophila* the Y chromosome is not involved in sex determination in the strict sense, since animals without a Y chromosome but one X chromosome are males (Bridges 1916) and animals with one or two Y chromosomes but two X chromosomes are females (Bridges 1916, Stern 1929). However, spermatogenesis in XO males does not lead to motile sperm and thus results in sterility (Bridges 1916, Shen 1932, Schultz 1947). In mammals the possible role of the Y chromosome in sex determination or male fertility is unknown. As in *Drosophila* the Y chromosome is without influence on sex in the plant *Rumex acetosa* (Ono 1935).

The existence of Y-linked inheritance in man was first suggested by Castle (1922) and Enriques (1922), after Schofield (1921) had described a pedigree of unusual inheritance of webbed toes. Castle, referring to the then recently published work on Y-linkage in fishes, pointed out that "Schofield's article furnishes evidence that the Y chromosome type of inheritance occurs in man as well. . ." Gates, in his book *Heredity and Eugenics* (1923), accepted this explanation. The revised edition, published under the title *Heredity in Man* (1929) mentions the Y chromosome in connection with webbed toes as wells as other pedigrees of human abnormalities. Haldane (1932) referred in passing to Y-linked inheritance of webbed toes, the skin abnormality of the Lambert family of "porcupine men", and "very probably" certain types of hypospadias. A more detailed treatment was given by Cockayne (1933) who listed Schofield's webbed toe pedigree under the section-heading "Sex-linked Y-chromosome Inheritance (Holandric)"[3] and stated that he knew "of only three other pedigrees which are most easily explained by assuming the presence of a dominant gene in the Y-chromosome." These three included the Lambert family, families with a skin defect called keratoma dissipatum and a family with hypertrichosis of the ears.

Incomplete sex-linkage in *Aplocheilus*, based on crossing-over between homologous

[3] The term holandric was coined by Enriques (1922) to describe a type of inheritance in which all males are affected and in which females neither exhibit the trait nor transmit the underlying gene. The only example in any organism known to Enriques was that of the Schofield family.

segments of the X and Y chromosomes, had been discovered by Aida (1921) and was soon found in some other animals. Haldane, in 1936, reported on the results of "A search for incomplete sex-linkage in man". The paper has stimulated much further work but the existence of this type of inheritance in man has increasingly become doubtful (Morton 1957). The present review will only be concerned with pedigrees which seemed to permit an interpretation in terms of complete Y-linkage. For the sake of simplicity the adjective "complete" will usually be omitted.

When, in 1946, Gates published his compendium on Human Genetics—invaluable as a source book, in spite of errors which few could have avoided in a task this size—he listed 14 traits under the heading "Genes in the Y." (p. 82-83). These were the following, in Gates' wording with a running number added as well as a reference to the page on which they will be considered below:

1. Ichthyosis hystrix (p. 161)
2. Black hairs in the ears (p. 158)
3. Webbed toes (p. 158)
4. Coloboma iridis (?). Sedgwick's case (p. 151)
5. Cataract (?). Harman's case (p. 154)
6. Keratoma dissipatum (3 fams.) (p. 156)
7. Peroneal atrophy, 1 case of cross-over, X—Y (p. 151)
8. Epidermolysis bullosa simplex (Yaffe) (p. 152)
9. Radio-ulnar synostosis (1 ped.) (p. 152)
10. Hyperextensibility of thumbs? (1 ped.) (p. 154)
11. Hypermobility of joints (1 ped.) ? (p. 154)
12. Blue sclera and brittle bones (1 ped.) (p. 154)
13. Adherent tongue (possible) (p. 155)
14. Camptodactyly (1 ped.)? (p. 153)

For a few other traits the possibility of Y-linkage is mentioned later in the text but apparently none seemed sufficiently likely candidates for this category to be included in the foregoing catalogue. It is seen that the 14 traits listed include one in which "1 case of cross-over X — Y" is noted. Otherwise the intent of the table would seem to have been a listing of only completely Y-linked genes since it does not contain any of the genes considered as partially sex-linked at that time. Most of the 14 traits listed in 1946 do not appear any more in Gates' (1954) summary of human linkage data. The only ones left are those numbered 1, 2, 3, and 9 above with a new one added:

15. "(probably) foot ulcers" (p. 155)

The most recent tabulation of Y-linkage in man, in the *Handbook of Biological Data* (1956) consists of items 1, 2, 3, and 6 plus:

16. "Color vision anomaly" (p. 162)

The following survey will be concerned with all sixteen traits though at different length. An additional trait:

17. "Abnormality of the external ear" (p. 163)

will also be included. Hypospadia will not be considered. Sörensen (1953) provides evidence that genes for these male-limited abnormalities are transmitted by both sexes.

CRITERIA FOR ABSOLUTE Y-LINKAGE

In its simplest form absolute Y-linkage results in all sons and none of the daughters of an affected male being affected. Two main kinds of exceptions from this expectation can be envisaged due to (a) incomplete penetrance and (b) non-disjunction of the sex chromosomes. With incomplete penetrance some sons may appear to be not affected while all daughters would obey the basic expectation that they are not affected. With non-disjunction, zygotes with one X chromosome but without a Y chromosome (XO) and others with two X chromosomes plus a Y chromosome (XXY) could be formed. In Drosophila XO individuals are males and XXY individuals females. Obviously such exceptional males do not inherit the Y-linked gene from their father while the exceptional females do. In man, it is not known whether XO and XXY zygotes would develop into males and females, respectively. If they do, exceptions from typical Y-linkage could be expected.

As will be seen later, all traits suspected as being based on Y-linked genes are so rare that only very small numbers of relevant individuals have been recorded. When, in these pedigrees, deviations from Y-linkage are encountered they may be taken rather as raising doubts as to the existence of this type of inheritance than as legitimate exceptions from it. Non-disjunction is a rare process whose occurrence may be looked for in large collections of data only. Its apparent presence in one or a few out of a very limited total of families should immediately suggest a search for some other explanation than Y-linkage.

Incomplete penetrance is a frequent phenomenon. If it occurred in the manifestation of a Y-linked gene it would tend to obscure the existence of its localization in the Y-chromosome. Instead of only affected sons from affected fathers non-affected sons would appear, in proportions depending on the frequency of penetrance. Such sibships would simulate segregation for a dominant autosomal gene. The daughters, of course, would remain uniformly non-affected but, with small data, the possibility would be considerable that autosomal segregation would, by chance, not have caused the production of affected females.

Even if the data do not offer any exception from expectation for complete Y-linkage other types of explanations must be explored. A simple possibility is that an autosomal dominant gene is responsible for the trait under discussion and that the observed presence of the trait in all males and its absence in all females is nothing but the result of chance. Another possibility is that the trait is again due to an autosomal dominant gene but that its expression is limited to the male sex. In this case one would still have to assume that its presence in all males of a given sibship is the product of chance but the absence of its expression in females would be the expected result of its sex limitation. While half of the male progeny of half of the females should of course be affected by the expression of a dominant autosomal gene carried by the mothers the number of such progeny-tested females would have to be considerable to be of sufficient bearing on the alternative Y-linkage or autosomal inheritance in case of absence of affected sons.

In Y-linkage the probability of obtaining only affected males and neither affected nor transmitting females is 1. In contrast, the probability of such a finding in autosomal dominance with or without sex limitation will always be smaller than 1. This,

however, does not mean that it is a more likely hypothesis to assume Y-linkage than either one of the two other types of inheritance. The *a priori* probability of finding a gene in the Y chromosome is small. Not only is the Y chromosome one out of 23 (or more) chromosomes of the set, and not only is it one of the smallest chromosomes, but all evidence from mammalian genetics speaks against it being a frequent carrier of completely Y-linked genes. No such gene would have likely been overlooked but none has been discovered in the extensive experimental work with mice, rats, guinea pigs, rabbits, cats, dogs, and other experimental or domesticated animals.[4]

It is hardly possible to assign a quantitative value to the *a priori* probability of finding a Y-linked gene in man, but it may well be of the order of the probability of finding a segregation for a dominant autosomal gene which among 10 or 12 individuals appears to be distributed to all males and to no females.

Finally, there is the problem of selective recording of holandric pedigrees. If the trait concerned is frequently encountered in pedigrees with an autosomal dominant type of inheritance special emphasis may be placed on an occasional holandric appearing kindred. Even a family some of whose members exhibit a unique trait may have a higher probability of being made the subject of a publication if all males of one or more sibships are affected and no females than if there were no apparent correlation of the trait with sex.

ANALYSIS OF 17 PRESUMABLY OR POSSIBLY Y-LINKED TRAITS

The seventeen cases whose inheritance has been ascribed to a completely Y-linked gene carry individually different weight. In some there is evidence at the onset against Y-linkage. In others, the possibility of Y-linkage deserves more careful consideration. The cases with *prima facie* evidence against Y-linkage will be discussed first.

Coloboma iridis

A single pedigree, reported by Streatfield (1858) after Sedgewick (1861), contains six bilaterally and one unilaterally affected male, in three generations. One male sib of affected persons is normal as are four female sibs of affected males. The only one of these females who was recorded as having had offspring was the mother of three affected sons. This is clearly not a case of Y-linkage.

Peroneal atrophy

In an extensive pedigree of peroneal atrophy (Herringham 1889, after Gates 1946) with otherwise typical complete recessive X-linked inheritance there was one sibship of two with an affected son and a carrier daughter. The father was affected. "This case of direct transmission from father to son could be explained by crossing-over between the X and the Y chromosomes so that one of the father's germ cells carried the gene in the Y." (Gates 1946 p. 967). Whether this or another explanation is valid, complete Y-linkage is excluded.

[4] Eichwald and Silmser (1956) have described a more rapid rejection by female recipients of skin grafts from male than from female donors of inbred strains of mice, a difference which conceivably could be attributed to a specific affect of the Y chromosome. Fox (1956) has rightly pointed out that this is not the only likely explanation.

Epydermolysis bullosa simplex

Yaffe's extensive pedigree (Yaffe 1942) contained originally 13 affected males descended in three generations in the male line from an affected man (Fig. 1). No normal male sibs were present. All seven female sibs were unaffected, but there was no information on their offspring, if any. This seemed to constitute one of the strongest cases for Y-linkage. Fortunately, the history of the family was followed up by Gates. In a footnote, he reports (1946; p. 299) that "correspondence elicits the further information that the normal sister (III-9) of four affected brothers had three normal daughters and an affected son. Hence the gene crossed over from the Y to the X chromosome."

The disease is usually caused by a dominant autosomal gene with not fully complete penetrance. Yaffe's kindred may have been a selected case of this type with the "improbable" sex distribution of the trait being due to chance. Complete Y-linkage is ruled out by the information quoted.

Radio-ulnar synostosis

Davenport, Taylor and Nelson (1924), presented a large pedigree of four generations with bilateral radio-ulnar synostosis occurring in three generations with 12 affected males and 12 not affected female sibs. One affected man had, in addition to two affected sons, also an affected daughter and a non-affected son. Gates (1946) comments that "this sibship can be explained on the assumption of crossing-over

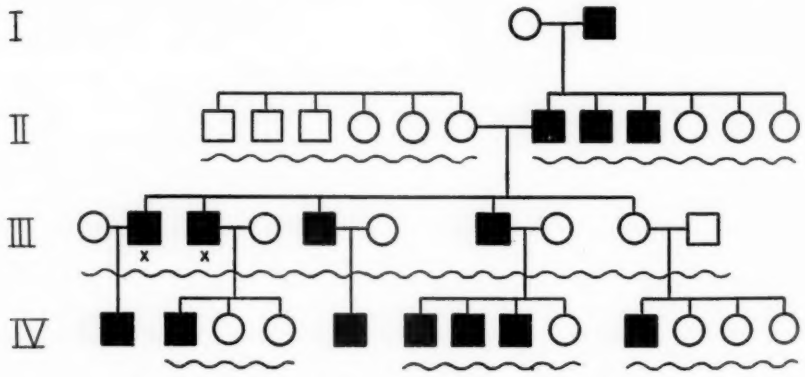

FIG. 1. EPIDERMOLYSIS BULLOSA. AFTER YAFFE AND GATES (1946).

Symbols used in this and later figures:
↗ propositus
X individuals seen by the investigator
~~ sequence within sibship not stated.
Numbers within enlarged male or female symbols indicate number of such individuals.
Numbers below symbols indicate ages.
This and the following pedigrees either have been redrawn from those given by the original investigators and usually include some additional information, or have been constructed from their statements.

from Y to X . . ." In any case, the presence of an affected daughter removes the trait from the category of complete Y-linkage.

Camptodactyly

Fantham's pedigree (1924) begins with an affected man and his normal wife and contains 10 affected males and 12 non-affected females in four generations descended in the male line from the initial couple (Fig. 2). No offspring is recorded for any of the females and there were five normal male sibs of the 10 affected males. One of the normal males had two sons and two daughters, all normal.

The trait, bent little finger, was incompletely penetrant within the same individual, being manifest on the left hand only (in *all* affected individuals?). Given such intra-individual incomplete penetrance it may be assumed that some of the normal individuals also carried the genetic basis of camptodactyly which remained unexpressed on both hands. An autosomal dominant with absence of affected females either due to chance segregation or non-penetrance appears a more likely explanation than Y-linkage.

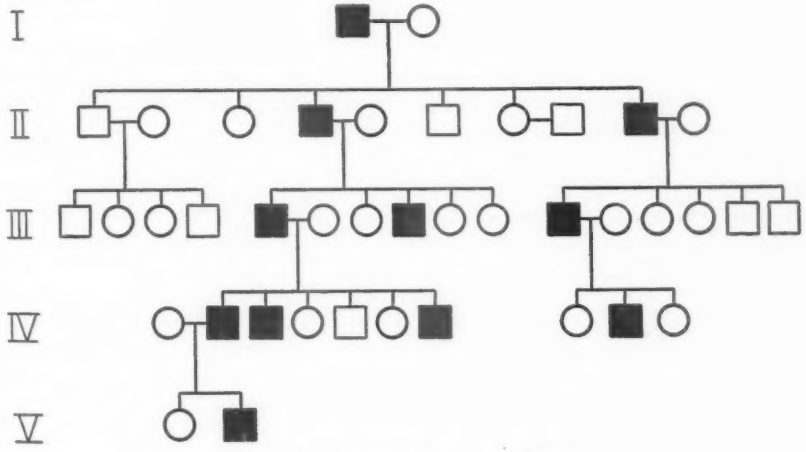

FIG. 2. CAMPTODACTYLY. AFTER FANTHAM.

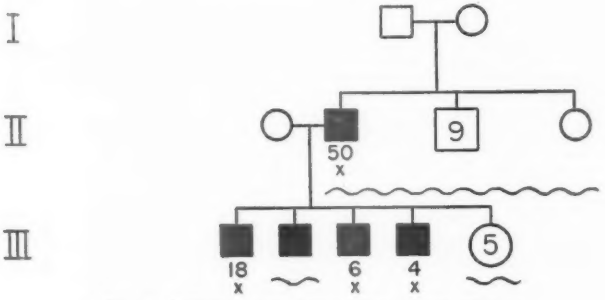

FIG. 3. HYPERMOBILITY OF JOINTS. AFTER KEY.

Hyperextensibility of thumbs; Hypermobility of joints; Blue sclera and brittle bones

Under the heading "Hypermobility of joints as a sex linked hereditary characteristic" Key (1927) described a family tree of three generations (Fig. 3). Beginning with a normal couple, the second generation consisted of nine normal males and one normal female plus one male who showed hypermobility of joints. This man had five normal daughters and four sons all of whom had hypermobility and bilateral clubfoot of two different types. One aspect of the "hypermobility of joints" is "hyperextensibility of thumbs". Gates (1946) deals with the same family under both headings, in different chapters (pages 797 and 448). Evidently by some error, (Key mentions that abnormal mobility of the joints is a feature in brittle bones and blue sclera) the family is described a third time by Gates as having contained the syndrome "brittle bones, blue sclera and hypermobility of the joints" (p. 767). This earned it a third listing among Y-linkage under the heading "blue sclera and brittle bones". The "three" suspected cases of Y-linkage thus were really a single one.

The genetics of clubfoot is complex. It often has been considered as due to a recessive gene, with incomplete penetrance, but also as due to a dominant, with incomplete penetrance. Clubfoot occurs about twice as frequently in males as in females. Key's case may be regarded as that of a syndrome in which clubfoot and hypermobility are different aspects of the same underlying defect. The affected father of the sibship of nine may be considered as a *forme fruste* in which clubfoot remained unexpressed. Perhaps he was heterozygous for an incompletely dominant gene for clubfoot and hypermobility which he transmitted to his four sons but either did not transmit to his five daughters or transmitted to some daughters where it was not penetrant. Since no offspring of any of the daughters is recorded, further light cannot be thrown on this question. As it stands, the family hardly contributes to the consideration of complete Y-linkage.

Cataract

In 1846, G. S. Dyer published a report under the title "Case of cataract in both eyes; occurrence of the Affection in the Males of three Generations" (see also Harman 1910). In reality, the pedigree (Fig. 4) shows three successive sibships II, III,

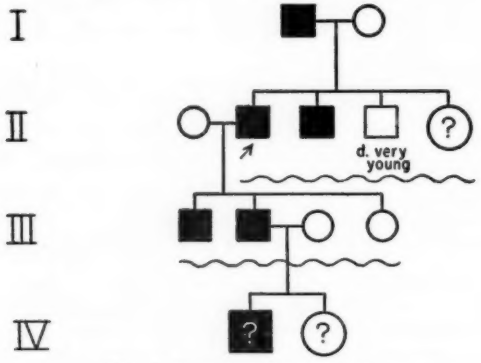

FIG. 4. CATARACT. AFTER DYER.

and IV containing affected males who are descended from an affected man in generation I. All males were affected (omitting one who died very young) and all females were normal. Apart from the first recorded male there are two affected males in II, two more in III, and an unspecified number of affected sons in the "large family" which forms the final sibship IV. There were "several" daughters in sibship II, one in sibship III and an unspecified number of daughters in the "large family" IV. One may conclude that there were more than six affected males and more than six normal females—probably considerably more of both types. No offspring of any of the females is noted. Cataract is normally inherited as a simple autosomal dominant and very many pedigrees have been recorded. It seems wisest not to single out one pedigree in which by chance ordinary autosomal transmission may have led to the appearance of holandry.

Adherent tongue

According to Weiss (1929) whose father, a professor of orthodontics, provided him with the information, a young man with a speech defect was observed who was not able to "elevate the tongue to make contact with the palate". The propositus reported that he had three brothers all of whom had a speech defect (one slight, one medium, and one severe) and four normal sisters (Fig. 5). His father also had a medium speech defect. The father had three brothers, one affected about the same as himself, and two very severely affected, and four normal sisters. A reference to an affected uncle fails to make it clear whether this was one of the father's brothers or another individual. Omitting this male there were eight males with speech defects and eight normal females, a much more significant distribution than that of four affected males and four normal females given by Gates (1946) who omits the sibs of the father (apart from the "uncle"). No offspring of the females is recorded. The pedigree is suggestive of Y-linkage but the trait involved is an unreliable one. The term "adherent tongue" is not founded on an anatomical diagnosis and it is not known whether a limited mobility of the tongue was the cause of the speech defects of any of the persons other than the propositus. The variable degree of the defect among the males raises the question of possible sex limitation or sex control so that females would not manifest it or do so more rarely even if the genetic basis were present. Again, little weight can be assigned to this trait in its bearing on Y-linkage.

Foot ulcers

A family with some members affected by neurotrophic osseous atrophy leading to ulcerations of the soles of the feet was described by E. M. Smith (1934; Fig. 6.)

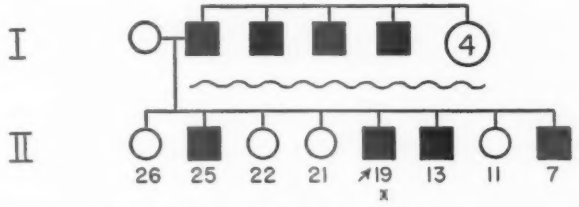

FIG. 5. ADHERENT TONGUE. AFTER WEISS.

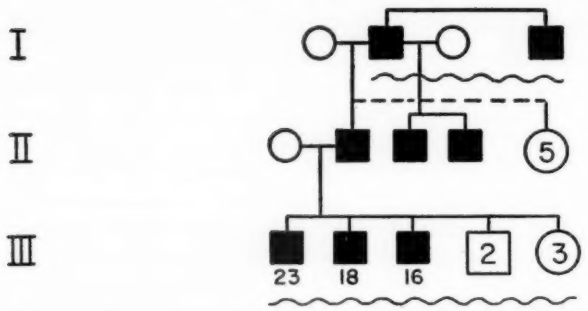

FIG. 6. FOOT ULCERS. AFTER E. M. SMITH. IT IS NOT KNOWN HOW THE FIVE FEMALES OF II WERE DISTRIBUTED OVER THE TWO MARRIAGES OF I-2.

Eight males were known to have been affected in three generations and five female sibs of the affected males in generation II were normal. In the last generation there were three affected males as well as two normal brothers and three normal daughters.

Unfortunately, the age or birth order of the sibs in generation III was not given. The defect develops only during the second decade of life. If the two normal brothers (and their three sisters) were too young to have shown the defect they can be disregarded, but if they were old enough their normal condition would not be compatible with Y-linkage. Dr. Elmer Maurice Smith died in 1946, so that no information additional to that published could be obtained.

The pedigree offers the same problems as several others in this series. It fits Y-linkage (if the five normal sibs of generation III are disregarded) but can also be considered a case of extreme deviation from the transmission of an ordinary autosomal dominant. Sex-limitation is not excluded since no information is available on offspring of the normal women in generation II.

Keratoma dissipatum

This skin defect is one of the four traits which Cockayne recognized as Y-linked. Gates (1946) reported on three families with the defect, the first one described by Brauer (1913), the second by Junghanns (1922) and a third whose source is not given. The detailed account of the "third" family makes it certain that it is none other than that of Brauer's which thus has been used twice.

The published information on Junghanns' family is given in a report on a meeting of a regional German dermatological association. Translated into English the part containing Junghanns' contribution reads as follows:

> "Junghanns: Keratoma hereditarium dissipatum palmare et plaetare (sic) (Brauer) in a 53 year old man which began in his 20th year and remained stationary in the last years. Inheritance in the male members of the family in the third generation."

Clearly, no conclusion can be drawn from such limited data.

This leaves only the first family for serious consideration. The original pedigree comprises four generations (Fig. 7). Since, however, all members of the last generation were too young to have developed the lesions even if they possessed the defective

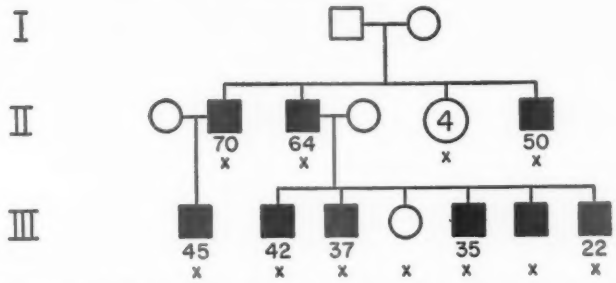

FIG. 7. KERATOMA DISSIPATUM. AFTER BRAUER. GENERATION IV HAS BEEN OMMITED SINCE ALL INDIVIDUALS WERE TOO YOUNG TO HAVE BEEN ABLE TO SHOW THE CONDITION.

genotype, they do not contribute to the understanding of the inheritance. The first generation (I) consisted of two normal parents. They had seven children (II), three affected sons and four normal daughters. Two of the sons had jointly six affected sons and one normal daughter (III); the third son left no offspring. The four normal daughters of generation II had, altogether, eight sons and four daughters, all normal (III).

This is an interesting pedigree not only because all nine males of generations II and III were affected and all females not affected but also because it seems to be a case where one of the parents of generation I was a genetic mosaic. Since both parents were somatically normal but produced three sons each of whom have received a mutant abnormal gene, part or all of the gonads of one parent must have carried the mutant. This situation makes it impossible to state whether the four females of generation II were normal because the keratoma gene never is transmitted to females, or whether only germ cells from a non-mutant gonad or a non-mutant sector participated in their conception.

The case would be weakest as an indicator for complete Y-linkage if the four females of generation II were omitted from consideration. In this case the relevant individuals would be the total of nine affected males and the one normal sister in the six children sibship of generation III.

The case would be strongest in favor of the interpretation of Y-linkage if it were assumed that all seven sibs of generation II came from a mutant region of the gonads of the mosaic parent. In this case there would be 14 relevant sibs in two generations consisting of nine affected males and 5 normal females. If an autosomal dominant gene were involved the probability of this sex distribution would be very small.

A skin defect, keratoma maculosa, which depends on an autosomal dominant gene is known from fourteen families (Cockayne 1933). Keratoma dissipatum is clinically and histologically indistinguishable from keratoma maculosa. Why then has it been separated from this more frequent condition and given a special name? The only reason is the holandric heredity of the trait in the Brauer family. This seems to be a paradigm of selective recording in human genetics. The probability of finding a pedigree with a holandric sex distribution of a trait must be viewed in relation to the total number of pedigrees of the trait. If one, or two, pedigrees, with holandric

distribution are placed into a separate category then they appear to be unique. If they are considered together with many other pedigrees their apparent uniqueness can be viewed as an extreme deviation from a sex-independent distribution.

These arguments are not decisive in an absolute sense. They leave open the alternative: autosomal dominant versus Y-linked gene. But they remove keratoma dissipatum from its relatively secure position in the list of Y-linked genes.

Hypertrichosis of the ears

Tommasi's (1907a, b) pedigree of a family in which all ten male descendents in the male line from an affected male ancestor and none of the seven female descendents had ears whose rims and surfaces were strikingly covered with long hairs has, since Cockayne called attention to it, seemed to represent rather strong evidence for complete Y-linkage (Fig. 8A). A reading of the original descriptions raises considerable doubts. Minor doubts arise in connection with the individuals of the last generation (V). There were two not affected brothers (not twins as in the pedigree constructed by Gates, 1946). This normality is not significant since the boys were too young to show the condition. However, it opens the question how many of the four females in generation V had reached an age in which they would have shown the hairiness provided it could appear in women. There are no data on record and the birth order of the sibs is also unknown. Graver doubts relate to the reliability of the pedigree as a whole. The propositus, III-6 and his wife III-7, were the only individuals personally seen by Tommasi and all information on the other members of the five generation pedigree comes from them. But III-6 was 81 years old when questioned and an inmate of a mental institution. It was at least the fourth time that he had been hospitalized for periods of four or more months at a time, for such conditions as alcoholism, psychomotor excitement, and religious delirium, at the ages of 42, 52, 55, and 81 years. His parents and other close relatives were also alcoholics and mentally abnormal. It may well be asked how much confidence can be based on such sources of information.

Gates (1957) has recently observed in Indians several new cases of similar hypertrichosis as that of Tommasi's patient. Gates also points out that the trait has been described in some other Italian individuals. It may be a not-too-rare characteristic. All affected individuals were males and in four cases more than one man occurred in a sibship or in successive generations (Fig. 8B–E). The data are fragmentary and no offspring from normal female sibs of affected males have been recorded. There is no evidence against complete Y-linkage of the characteristic and further studies should be attempted. On the other hand, hypertrichosis of the ears may be suspected to be male sex-limited, independent of Y-linkage. It may well be in the same class as growth of hair in the external auditory meatus of older men, or the growth of the beard. In this case, one would expect unaffected women to transmit the trait. Until evidence is available on this question judgement may well be postponed.

Webbed toes

Schofield's (1921) pedigree (Fig. 9) of webbed toes in his own family shows 13 affected male descendents in the male lines from an affected man (I-2), 11 not af-

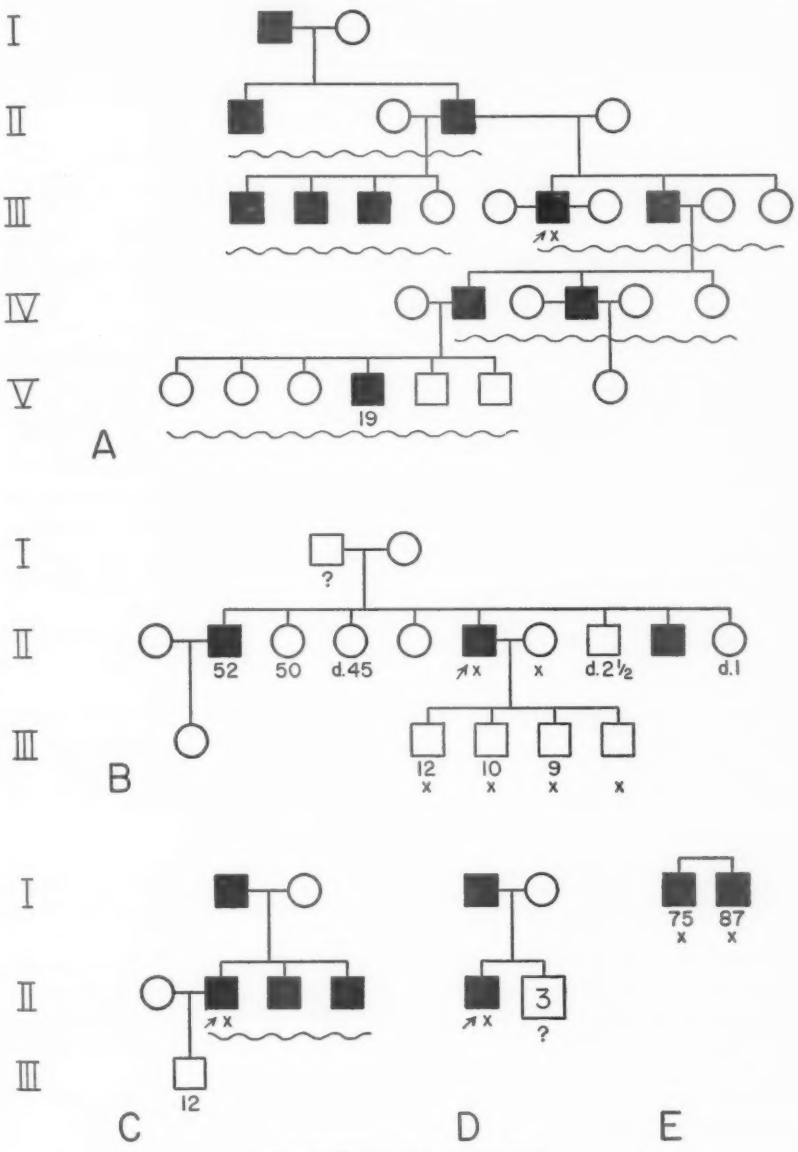

FIG. 8. HYPERTRICHOSIS OF EARS.

A. AFTER TOMMASI. V-5 AND V-6 EITHER WERE YOUNGER THAN V-4 OR DIED BEFORE AGE 19.
B-D. AFTER GATES (1957).
E. AFTER CAINER (1898).

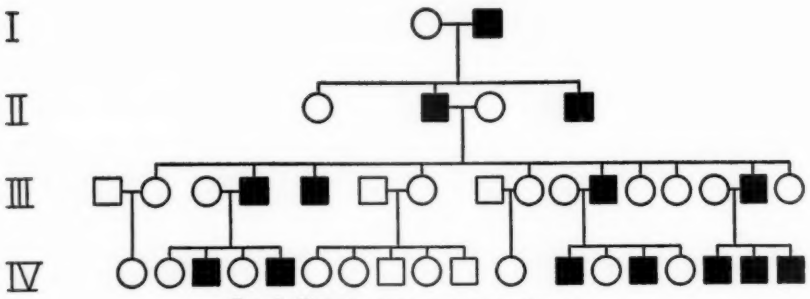

FIG. 9. WEBBED TOES. AFTER SCHOFIELD.

fected female sibs of affected brothers and a total of two normal sons and five normal daughters in the progeny of three not affected female sibs of generation III. By itself the pedigree not only is fully in accord with an interpretation in terms of complete Y-linkage but deviates widely from the random sex distribution of affected persons to be expected from an autosomal dominant. Yet, there are reasons for hesitation.

The original publication was extremely brief. No details were given regarding the sources of information for the designations "affected" and "not affected". The degree of webbing was described as variable and two outline drawings of feet accompanied the article but it remained obscure whether the decision webbed or not webbed was always clear-cut or whether borderline cases were encountered.

Enriques, in 1924, concluded a critical discussion of Schofield's note with the following paragraph:

> "At any rate, Mr. Schofield has caused us to be somewhat embarrassed with this single pedigree, so small and so strange. Since he tells us that just in his family he has seen such traits, there is nothing left for us but to respectfully urge him and all members of his family, male and female, to produce many children, many male children and many female children, for the love of science. Then in twenty or thirty years, the Lord willing, we shall be able to ascertain the importance of this point on the theory of heredity."

Attempts by the writer of the present review, who then was unaware of Enriques' suggestion, to visit Dr. R. Schofield and to obtain addresses of a few members of the family were politely discouraged (exchanges of letters in 1948, 1956). Thus, the opportunity has been denied for restudy of some of the individuals in this important pedigree of 1921, and to investigate additional members of the family. All those who have been born in the intervening decades have shown, according to Schofield (letter to the writer, 1948), as far as his knowledge went, the same characteristic lines of inheritance as in the original family material.

Webbing of toes is known from extensive other pedigrees and usually follows the transmission of an autosomal dominant gene. Penetrance is frequently incomplete and rarer in the female than the male sex. On the basis of these facts Gates expresses the opinion that an autosomal dominant may be involved in all cases, including that of the Schofield family. An unpublished study of Professor F. E. Stephens from Utah, kindly made available to the author, is particularly relevant to this interpretation. In a large kindred webbed toes seemed at first to be typically holandric in distribu-

tion. Further search, however, uncovered some non-affected males and one affected female. The manifestation of webbing apparently was mostly suppressed in the female sex and the surplus of affected over non-affected males was a chance phenomenon.

It is regrettable that the first human trait which has been regarded as due to a completely Y-linked gene must at present remain in the group of undecided cases.

Ichthyosis hystrix

The "porcupine men" of the English Lambert family have been famous ever since the first one was presented before the Royal Society in 1731. Cockayne, in 1933, compiled a pedigree in which twelve affected males are entered in six consecutive generations together with seven not-affected female sibs (Fig. 10A). An intensive restudy of the original literature and a search of the parish registers of births, christenings, marriages and burials has led to a radical re-evaluation of the evidence for holandric inheritance of the porcupine trait (Penrose and Stern, in preparation). It has become clear (Fig. 10B) (a) that the only affected individuals for whom reliable records exist were four males, in generations II, III, and IV; (b) that there were two females and three males among the five sibs of III-2; (c) that the sibship of generation IV consisted of at least six instead of two males, one probably unaffected, and probably only one instead of seven females; and (d) that the two affected males of

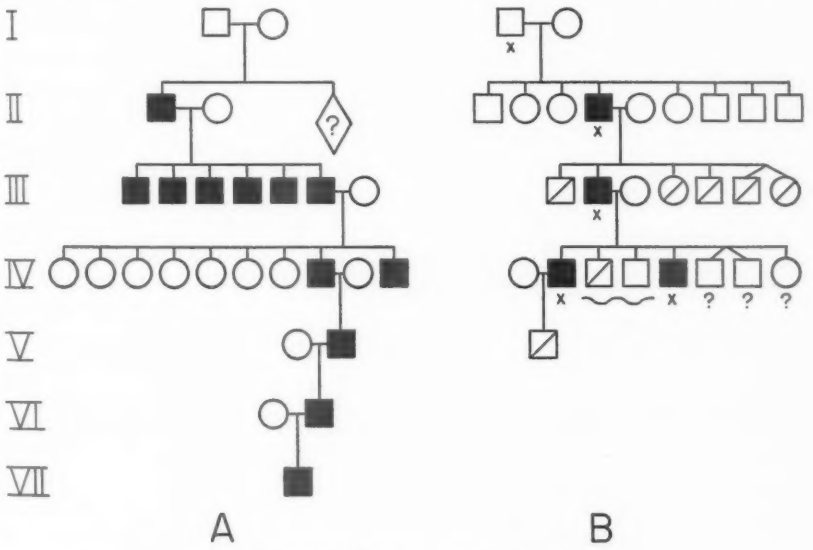

FIG. 10. ICHTHYOSIS HYSTRIX, THE LAMBERT FAMILY.

A. AFTER COCKAYNE.

B. AFTER PENROSE AND STERN. SYMBOLS WITH AN OBLIQUE LINE INDICATE THAT THESE INDIVIDUALS WERE REPORTED TO HAVE BEEN AFFECTED. THE WAVY LINE IN IV INDICATES THAT THE SEQUENCE OF IV-3 AND IV-4 AMONG THEMSELVES IS UNKNOWN. THE ZYGOSITY OF THE TWINS IN IV IS UNKNOWN. THE QUESTION MARKS SIGNIFY ABSENCE OF INFORMATION CONCERNING TRAIT.

generations V and VI have actually never been recorded and had been entered in the pedigree due to misreading of earlier accounts. If the recorded statements of II-1 that *all* his children had been affected are accepted then the fact that two of them were girls eliminates further consideration of Y-linkage. If, on the other hand, only individuals are considered who were seen by competent students then all that is left are four affected males. Only a selective elimination of the two females III-4 and III-7 and of the male IV-4, but a retention of other equally unascertainable members of the family would decrease again the probability for inheritance of an autosomal dominant but certainly not enough to re-establish the case for Y-linkage.

A similar though less spectacular family group of ichthosis hystrix has recently been investigated by Curth and Macklin (1954). Here females as well as males were affected though clearly much milder than the males. It is possible that the Lambert family carried a similar autosomal dominant gene as the one in this family.

Color vision anomaly

S. C. Reed, Cambier and Applen (1951) have given a short report on the family of the second of the three authors, in which an anomaly of color vision is stated to have been present in all ten males descended in the male line from an affected man and have been absent in all five female descendents in the male lines (Fig. 11). None of the total of five sons and four daughters of four of these five females were affected (the fifth woman remained childless). "Unfortunately it has not been possible to test the members of the family in a satisfactory manner." (Reed, et al.). The anomaloscope could not be used and at most five of the men were given pseudoisochromatic plate tests which showed them to be deficient. The authors themselves seem confident of the written or verbal statements of the members of the family "which were very definite. Each person was quite certain as to his or her possession, or lack, of a color vision anomaly." Yet the authors themselves begin their discussion of the inheritance with the careful phrase "If the evidence presented by the members of this family is accurate . . ."

If it is, then the authors calculate that the probability is negligible that the color vision anomaly of the Cambier family is of the usual X-linked type. (There is, of

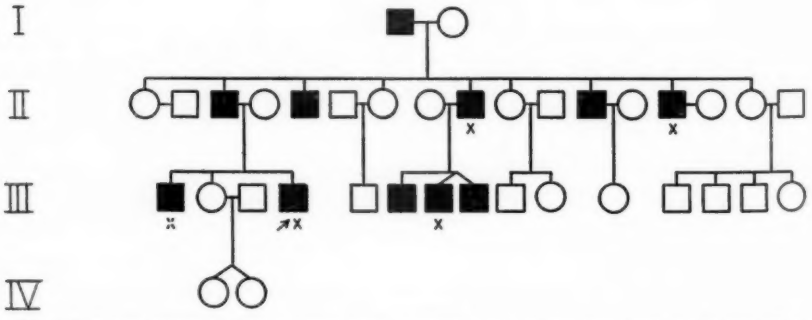

FIG. 11. COLOR VISION ANOMALY. AFTER REED, CAMBIER AND APPLEN. THE ZYGOSITY OF THE TWINS IN III AND IV IS UNKNOWN. THE TYPE OF COLOR TEST GIVEN TO III-1 IS NOT KNOWN.

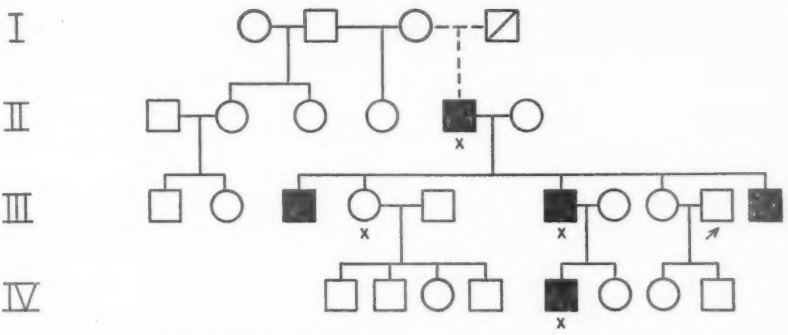

FIG. 12. ABNORMALITY OF THE EXTERNAL EAR. AFTER CROW (UNPUBLISHED). THE PATERNITY OF II-5 FROM I-4 IS CONJECTURAL. I-4 IS SAID TO HAVE BEEN AFFECTED.

course, insufficient information available as to the type of color defect present.) They also reject a hypothesis involving crossing over of a normally X-linked gene to the Y chromosome. They assume that the gene for color vision deficiency in the family represents a mutation in the non-homologous section of the Y chromosome.

There is no discussion of the possibility that an autosomal dominant gene may be involved. Such a gene may have been the basis of the color vision defect in the famous Cunier family (Stern and Walls, 1957). If really all evidence presented is to be accepted then the probability in favor of the reported sex distribution of the trait being due to chance segregation of an autosomal dominant is very small though much larger than that calculated for a recessive X-linked trait. One should hesitate, however, to base any definite conclusion on a pedigree which involves the type and amount of uncertainty as the one under discussion.

Abnormality of the external ear

Professor J. F. Crow has kindly made available for discussion here a pedigree involving an abnormality of the pinna, so that the external ear is greatly reduced in size and appears almost shell-like (Fig. 12). According to Crow's informant, a graduate student of the University of Wisconsin, the expressivity is quite variable though all individuals have clearly deviant external ears. Some have also a mild facial paralysis and one person had an unilaterally abnormal middle or inner ear.

The paternity of II-5 from I-4 is a matter of presumption based on an interpretation of some family tradition. The pedigree fits expectations from Y-linkage but, with rather low probabilities, also conforms to extreme segregations based on either an ordinary autosomal dominant or a male sex limited autosomal dominant. "My feeling about this is that it is a pedigree suggestive of Y-chromosome inheritance, but of course not conclusive." (letter from J. F. Crow, November 28, 1956).

CONCLUSIONS

The evidence for Y-linkage in man is at best ambiguous. The "best" pedigrees, taken by themselves, have only a low probability of being interpretable as the result of chance segregation of autosomal genes but such an interpretation becomes more

acceptable if one realizes that these pedigrees have been selected from thousands showing ordinary autosomal or X-linked inheritance. It is significant that, with the exception of hypertrichosis of the ears, each case of supposed Y-linkage is represented by a single family group. If there were really normal alleles in the Y chromosome of normal individuals then one might expect mutations to abnormal alleles to occur sufficiently frequently to be discovered in more than single pedigrees.

A decision not to accept any one of the known conditions as due to proven Y-linkage should, however, not be equivalent to a neglect to search for new evidence. One or another of the traits discussed may still turn out to be truly Y-linked. There may exist in the Y chromosome some normal genes with a very low mutation rate, or, as Haldane (1936) pointed out, the Y chromosome may occasionally receive, by translocation, genic material with morphologic expression from another chromosome. That the Y chromosome has a function of its own is attested by its very existence. What it is still must be discovered.

SUMMARY

An analysis of the evidence concerning sixteen traits formerly regarded as possibly or presumably being due to completely Y-linked genes and a new trait of similar inheritance leads to the conclusion that some pedigrees must definitely be excluded from complete Y-linkage. All others may be accounted for by assuming unusual sex distribution of an autosomal dominant gene due to chance or in addition by assuming sex limitation. For a few pedigrees the probabilities of the last assumptions are small and a final decision must await further data.

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Parental Age in Achondroplasia and Mongolism

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ADVANCED PARENTAL AGE has been known for a long time to be a feature in the etiology of achondroplasia. The peculiarity was first noticed by Weinberg (1912) and its existence amply confirmed by Mørch (1941). Until recently the question as to whether the effect is entirely maternal, as it appears to be in mongolism (Jenkins, 1933; Penrose, 1933), or of a different character has not been closely investigated. Data collected by Krooth (1952) and by Grebe (1944) indicate that the father's age is raised more than the mother's and the same was true in Mørch's material. A new survey of cases in Northern Ireland has recently been made by Stevenson (1957). In this investigation a control sample of parents was collected so that a direct estimation of the relative effects concerned with the father and with the mother could be made.

Stevenson's data on sporadic achondroplasia comprise 37 cases from the general population and 9 non-surviving cases discovered at birth. The two groups are probably not homogeneous clinically and no appreciable increase in parental age was found in the cases which did not survive. However, the bias of including them tends away from the hypothesis of etiological importance of increased age of the father. The combined group of 46 cases has therefore been used in the present calculations.

The simplest test uses the method of partial correlation as indicated by Wright (1926). There are three values to be calculated, (i) the ordinary product moment correlation (N × N) between father's and mother's ages, (ii) the correlation (N × 2) between father's age and incidence of achondroplasia, (iii) the corresponding correlation (N × 2) of mother's age with the incidence of achondroplasia. The results, for Stevenson's 46 achondroplasics and 46 controls, are given in table 1, where similar calculations previously made for mongolism are quoted. These two sets of data are comparable for the present purpose although the controls in the cases of mongolism were the unaffected members of the same families.

For achondroplasia the partial correlations, (iv) for constant maternal age and (v) for constant paternal age, indicate that the age of the father is the main factor. When the maternal age is held constant a significantly positive partial correlation (+0.273) is left between father's age and the incidence whereas, when paternal age is held constant, the effect of the mother disappears. This result is exactly contrary to that shown in families containing cases of mongolism where the relationship to the father's age is eliminated when the mother's age is held constant.

It is easy to appreciate the difference between the results for (a) and (b) if the mean parental ages of normals and abnormals are directly compared. This could be an equivalent test if the standard deviations of paternal ages, in the general populations used for controls, were always available. Information derived from previous surveys

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TABLE 1. CORRELATIONS OF PATERNAL AND MATERNAL AGE WITH INCIDENCE OF (a) ACHONDROPLASIA (46 CASES, 46 CONTROLS), AND (b) MONGOLISM (154 CASES, 573 CONTROLS)

(a) Achondroplasia (Stevenson, 1957)	(b) Mongolism (Penrose, 1933)
(i) $r_{fm} = +0.793 \pm 0.039$	(i) $r_{fm} = +0.829 \pm 0.012$
(ii) $r_{fa} = +0.391 \pm 0.089$	(ii) $r_{fb} = +0.294 \pm 0.034$
(iii) $r_{ma} = +0.277 \pm 0.097$	(iii) $r_{mb} = +0.362 \pm 0.032$
(iv) $r_{fa.m} = +0.293 \pm 0.090$	(iv) $r_{fb.m} = -0.011 \pm 0.035$
(v) $r_{ma.f} = -0.084 \pm 0.098$	(v) $r_{mb.f} = +0.221 \pm 0.033$

N.B. f signifies paternal age, m, maternal age and a or b, incidence.

TABLE 2. EXCESS OF MEAN PARENTAL AGES OVER CONTROL POPULATION MEANS (a) FOR ACHONDROPLASIA, AND (b) FOR MONGOLISM

Source	Number of cases	Mean excess of father's age	Mean excess of mother's age	Control mean*
(a) Mørch (1941)	97	+5.4	+3.5	D
Krooth (1952)	16	+6.8	+5.7	E
Grebe (1955)	63	+4.3	+3.1	G
Stevenson (1957)	46	+7.2	+3.5	I
All	222	+5.6	+3.5	—
(b) van der Scheer (1927)	316	+5.9	+6.6	H
Schulz (1931)	80	+5.3	+7.7	G
Øster (1953)	369	+5.3	+6.5	D
Penrose (1955)	215	+6.8	+7.4	E
All	980	+5.8	+6.7	—

* Control means:

D (Denmark)	father, 33.3;	mother, 28.6
E (England)	" 30.9;	" 28.6
G (Germany)	" 32.6;	" 28.9
H (Holland)	" 33.7;	" 31.1
I (Northern Ireland)	" 31.6;	" 28.9

is summarized in table 2. The results all agree with one another. In every instance the effect of father's age is greater than the effect of mother's for achondroplasia and the converse is true for mongolism.

In mongolism, analysis of the question of birth order indicated that it is the age of the mother, not the parity, that is significant (Penrose, 1934). A similar analysis with respect to paternal age has not yet been carried out because of absence of published details about sibs but inspection of existing data strongly suggests that here again birth order is not the critical factor.

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On the Estimation of the Frequency of Genetic Carriers

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INTRODUCTION

IN THIS PAPER we shall employ the term 'carrier' to denote an individual who is heterozygous for a rare recessive gene. It is of interest to estimate the frequency of genetic carriers for four reasons:

Since persons heterozygous for rare recessive genes can sometimes express their heterozygosity (Neel, 1949) and since most persons are probably heterozygous for a number of such genes (Muller, 1950), the particular genes in each case varying greatly, heterozygosity for rare recessive genes may be an important cause of normal human variation. The extent to which any group of recessives can contribute to the polymorphism of the general population will depend on the frequency of their carriers.

If rare recessives are expressed to some extent in the heterozygote, it follows that natural selection may act on heterozygotes, favoring or not favoring the carrier. The role, at any given time, of selection on carriers in the determination of the equilibrium frequency of the disease will depend in part on the frequency of the carriers, or at least on the ratio of carriers to affected.

In the case of most rare recessive diseases, the greater number of affected are produced by two heterozygotes—persons who have the capacity, under suitable circumstances, of transmitting a disease which they themselves do not have. Thus heterozygotes are the immediate reservoir of the agent responsible for the disease, and their frequency seems to emphasize more sharply than the incidence of the disease itself the ubiquity of the fundamental pathogen.

In evaluating the genetic effects of ionizing radiation on human populations, theoretical arguments depend on the average total number of deleterious recessives for which the members of the community are heterozygous (Muller, 1950; Neel and Schull, 1956). This total can be estimated by simply summing the average number of deleterious recessives per person at each known human locus (Krooth and Neel, 1956). It can also be estimated from the frequency with which homozygous gene combinations occur among the children of consanguineous marriages (Reed, 1954; Slatis, 1954).

One of the obstacles that has often been encountered in the study of rare recessive diseases is the difficulty in determining whether all cases are homozygous at the same locus and in determining also whether precisely the same recessive alleles are involved in each case. In other words, a recessively inherited disease state, which clinically

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appears as a single entity, may sometimes result from homozygosity at several alternative loci, or, even at a single locus, may result from homozygosity for several alternatives alleles. For example, alternative loci or multiple alleles are probably involved in the genetics of Hurler's syndrome (Herndon *et al*, 1956), cystinuria (Harris and Warren, 1953), congenital deafness (Stevenson and Cheeseman, 1956), and perhaps non-endemic cretinism, von Gierke's disease, and the adrenogenital syndrome (reviewed by Childs and Sidbury, 1957). Other examples could probably be cited, and indeed there are only a few rare recessive conditions in which, on the basis of consanguinity figures, we can be sure there is but one locus and one allele.

It therefore seems of value to derive an expression for the frequency of persons heterozygous for one or more genes responsible for a rare recessive disease when the number of alternative loci or the number of alleles or both cannot be specified.

EXPRESSION FOR THE ESTIMATE OF THE FREQUENCY OF GENETIC CARRIERS

Some basic assumptions.

We shall obtain an expression for the frequency of carriers among the children of non-consanguineous unaffected persons in the population. After having obtained this expression, we might add terms to allow for:

1) the additional carriers contributed by consanguineous marriages,

2) the additional carriers contributed by the process of mutation,

3) the additional carriers contributed by marriages involving affected persons themselves, and

4) the carriers contributed or removed by natural selection in a single generation.

Let us now consider these terms in order:

1) We shall assume that the population is not highly inbred, and that most carriers, like most persons in general, come from matings that are not closely consanguineous. Even among the offspring of first-cousin marriages, the frequency of carriers will be nearly what one would expect on random mating.

2) We shall assume that the process of mutation, in each generation, contributes but a negligible proportion of carriers compared with the reproduction of other carriers.

3) We shall assume that the disease is sufficiently rare or debilitating that the affected persons themselves do not contribute appreciably to the frequency of carriers.

4) Without implying that selection on the heterozygote is unimportant in determining the equilibrium gene frequencies and without implying that the population is in equilibrium, we shall assume that the proportion of all heterozygotes which is added or subtracted by selection in each generation is, on the average, small. Since we are concerned with the case in which the heterozygote cannot be readily detected, this assumption is somewhat strengthened though not of course proven to be valid. The assumption would appear to hold, however, for a gene like the one for sickle cell anemia, although this gene is far more common than the ones we are considering, and we are able to detect sickle cell heterozygotes.

Finally, we shall assume that the disease is sufficiently rare that the size of the whole population is not diminished by the exclusion of *all* of the offspring of the

affected themselves so that the frequency of carriers among the children of unaffected approximates the frequency of carriers in general.

It should be noted that the four assumptions above are all implicit, in the case of a single recessive allele at a single locus, when one estimates the carrier frequency as $2b(1 - b)$ from the frequency of the homozygote b^2.

Algebraic argument

Let us suppose that we have a locus l_j with $[A_{ij}]$ dominant alleles such that i varies from 1 to f_j and $[a_{ij}]$ recessive alleles such that i varies from 1 to m_j . Suppose p_{ij} is the frequency of A_{ij} and q_{ij} is the frequency of a_{ij} among, in both instances, the chromosomes of all persons unaffected with the disease. Consider that there are n loci involved, in the sense that a person whose genotype is $a_{ij}a_{ij}$ or $a_{ij}a_{kj}$ at any one of these n loci has the rare disease.

What is the average number of the $[a_{ij}]$ genes carried per unaffected person? Let

I_j = the frequency of all cases of the disease due to recessivity at locus j among the children of unaffected parents.

I = the frequency of all cases of the disease among the children of unaffected parents.

k_j = the proportion, among all cases of the disease (from unaffected parents) due to recessivity at locus j, who come from first-cousin marriages.

k = the proportion, among all cases of the disease from unaffected parents, who come from first-cousin marriages.

c = the proportion, among all persons in the population from unaffected parents, who come from first-cousin marriages.

H_j = the frequency of persons heterozygous at locus j and H = the average number of the $[a_{ij}]$ genes, carried in unaffected persons, per unaffected person.

We may now write an expression for the frequency of carriers. The frequency of the several phenotypes among the children of non-consanguineous unaffected persons is obtained by expanding

$$[p_j + q_j]^2$$

for each locus j, where $\sum_{i=1}^{i=f_j} p_{ij} = p_j$ and $\sum_{i=1}^{i=m_j} q_{ij} = q_j$. At each locus j,

$$p_j^2$$

is the frequency of persons having no recessive allele,

$$q_j^2$$

is the frequency of persons having two (who of course are affected), and

$$H_j = 2p_jq_j$$

is the frequency of carriers, assuming here as in the preceding sentence that unaffected persons mate at random. We see that

$$H_j = 2(q_j - q_j^2).$$

Of the heterozygotes at locus j, a fraction, $Hj(I - I_j)$, will be affected, owing to homozygosity at some locus other than j. Thus $\sum_{j=1}^{j=n} H_j[1 - (I - I_j)]$ is the frequency, per person, of the $[a_{ij}]$ genes carried by unaffected persons, and

$$H = \sum_{j=1}^{j=n} H_j \, [1 - (I - I_j)] \, (1 - I)^{-1}$$

or the average number of the $[a_{ij}]$ genes, carried by unaffected persons, per unaffected person. Since, however, the disease is assumed to be rare, we may approximate by setting

$$H = \sum_{j=1}^{j=n} H_j . \tag{1}$$

Assuming that the inclusion of the offspring of consanguineous marriages more remote than between first cousins in the general population does not occasion a significant departure from random mating, we have

$$16 \, I_j = c\left[\sum_{i=1}^{i=m_j} q_{ij} + 15\left(\sum_{i=1}^{i=m_j} {q_{ij}}^2\right)\right] + 16\,(1 - c)\sum_{i=1}^{i=m_j} {q_{ij}}^2\Bigg)$$

and

$$I = \sum_{j=1}^{j=n} I_j \tag{2}$$

$$k_j = \frac{c\left[\sum_{i=1}^{i=m_j} q_{ij} + 15\left(\sum_{i=1}^{i=m_j} {q_{ij}}^2\right)\right]}{16 \, I_j}$$

$$k = \frac{\sum_{j=1}^{j=n} k_j I_j}{I} . \tag{3}$$

Expressions for I_j and k_j can readily be derived by generalizing the Lenz consanguinity formula for the case of multiple alleles. A recent development of the Lenz formula is available in Stern (1950, page 347). Note that the expression for I_j given above assumes that the population incidence can be broken down into the sum of two terms. One term measures the contribution of first-cousin marriages and the other the contribution of unrelated parents.

Equations (2) and (3), after elementary substitutions, may be regarded as simultaneous equations in the two unknowns:

$$\sum_{j=1}^{j=n} q_j \text{ and } \sum_{j=1}^{j=n} q_j^2$$

Solution for these two unknowns and substitution of the values obtained into equation (1), leads to the result

$$H = \frac{32 \, I(k - c)}{c(1 - c)}$$

which, under the assumptions listed, holds for any recessive disease that is caused by a double dose of any one of m_j genes at any one of n loci, so that j varies from 1 to n. Moreover, at the j^{th} locus, there may be f_j different dominants allelic to the m_j recessives. The assumptions involved do not in any way constrain the number of loci or the number of alleles at each locus or the ratio of normal dominants to abnormal recessives at each locus. No assumption is made about the total number of alleles or about the total ratio of dominant to recessive alleles. Random mating is assumed to occur only among unaffected persons. The other assumptions which are employed are either analogous to those which obtain when estimating, by the Hardy-Weinberg relations, the frequency of carriers for a single recessive allele at a single locus from the frequency of affected homozygotes, or else they follow from the assumption that the disease itself is rare.

The above argument holds for all recessive genes which are of the classical type in the sense that a person whose genotype is $a_{ij}a_{ij}$ is affected. Most Mendelian genes seem to have this property—two different alleles capable of causing a disease in the homozygote can cause a comparable abnormality when one of each is present.

It is of interest to examine briefly the case in which this condition does not hold. We must then include in our expression for the mean number of recessives per unaffected person twice the frequency, among unaffected persons, of individuals whose genotype is of the form $a_{ij}a_{tj}$. We have

$$H_j = 2\left[q_j(1 - q_j) + q_j^2 - \sum_{i=1}^{i=m_j} q_{ij}^2\right],$$

or

$$H_j = 2\left[q_j - \sum_{i=1}^{i=m_j} q_{ij}^2\right], \text{ and again}$$

$$H = \sum_{j=1}^{j=n} H_j \tag{4}$$

$$k_j = c\frac{\left[q_j + 15\sum_{i=1}^{i=m_j} q_{ij}^2\right]}{16\, I_j}$$

and

$$k = \frac{\sum_{j=1}^{j=n} k_j I_j}{I} \tag{5}$$

and

$$16\, I_j = c[q_j + 15 \sum q_{ij}^2] + 16(1 - c) \sum q_{ij}^2$$

$$I = \sum I_j \tag{6}$$

Simultaneous solution of (5) and (6) for $\sum_{j=1}^{j=n} q_j$ and $\sum_{j=1}^{j=n}\sum_{i=1}^{i=m_j} q_{ij}^2$ and substitution into (4) leads to

$$H = \frac{32\, I\,(k - c)}{c(1 - c)}$$

which is precisely the same result as before. Therefore, it does not matter whether the double but non-homozygous recessive is or is not affected. The identity still holds.

Having now determined the mean number of recessives per normal person, what is the frequency of genetic carriers? We may assume that the proportion of normal persons carrying 0, 1, 2, . . . , × recessives determining the character obeys a Poisson distribution. Therefore the frequency of genetic carriers (persons carrying at least one such gene) is

$$1 - e^{-H}.$$

When H is small, $1 - e^{-H}$ is nearly equal to H.

It is of interest to determine, among the children of unaffected by unaffected matings, the ratio, R, of the number of recessive genes for the disease *in carriers* to the number of recessive genes for the disease *in affected*. The proportion, among the children of unaffected by unaffected matings, of all recessive genes for the disease which are in carriers, we shall call G, and

$$G = \frac{R}{1 + R}.$$

If the disease is rare, as we have assumed, and especially if it is disabling, G will yield a good estimate of the corresponding proportion among all children.

Let N = the total number of children from unaffected by unaffected matings; then HN = the total number of genes in children (from these matings) who are carriers and 2NI = the total number of genes in children (from these matings) who are affected. Hence

$$R = \frac{H}{2I} = \frac{16(k - c)}{c(1 - c)}.$$

VARIANCE OF THE ESTIMATE OF THE MEAN NUMBER OF RECESSIVES PER UNAFFECTED PERSON

Assuming that I, k, and c are estimated as ordinary binomial proportions, an adequate approximation of the variance of H can be obtained, in reasonably large samples, by

$$\text{var}\,(H) = \frac{1024\,I}{c^2}\left[\frac{(k - c)^2(1 - I)}{n_I} + \frac{Ik(1 - k)}{n_k} + \frac{Ik^2}{cn_c}\right]$$

where c is assumed to be small and where

n_I = the total number of observations I is based on;

n_k = the total number of observations k is based on; and

n_c = the total number of observations c is based on.

The variance of the estimate of the frequency of genetic carriers is approximately e^{2H} var (H), assuming var (H) is small.

Example. Stevenson and Cheeseman (1956) considered briefly the problem of

estimating the frequency of genetic carriers in their excellent investigations of congenital deafness. There is evidence that idiopathic congenital deafness is determined by recessivity at any one of several loci. The consanguinity rate is too high for a single gene, yet, after correcting for ascertainment, they find that among unaffected by unaffected consanguineous matings, which have yielded at least one abnormal, the proportion of abnormals is $\frac{1}{4}$. Matings of deaf by deaf, considering only idiopathic deafness, resulted in either all deaf, all hearing, or *both hearing and deaf* offspring. Stevenson and Cheeseman consider this latter result evidence favoring alternative loci. At least one partner in the mating of deaf by deaf which produces both kinds of offspring is supposed to be homozygous at one locus and heterozygous at another. (There were 5 out of 32 fertile non-consanguineous deaf by deaf matings in their data, which yielded both kinds of offspring.) Two different mechanisms (at least) may account for the presence of both deaf and hearing offspring from deaf by deaf matings. For one thing, the two parents may be heterozygous at an identical locus, in addition to being homozygous at different loci. Since hereditary deafness is rare, this explanation is unacceptable, for the proportion, of all deaf by deaf matings, producing both sorts of offspring should be somewhat *less* than the proportion, of all unaffected by unaffected matings, having both sorts of offspring, the deaf having fewer loci at which to be heterozygous. The other mechanism also assumes the two parents are homozygous at different loci, but one parent is, in addition, heterozygous at the locus for which the other parent is homozygous. By this mechanism, the proportion of all deaf by deaf matings producing both kinds of offspring should be considerably greater.

The authors mention the high frequency of the genetic carriers of deafness. They compute the frequency of the gene for deafness in a way which gives a better estimate of the frequency than simply taking the square root of the incidence of the disease among the children of all unaffected non-consanguineous parents.

They estimate the proportion of all fertile deaf by hearing (or deaf by acquired deaf) matings, which contain both deaf and non-deaf offspring. (It is interesting that out of 6 such families, one was consanguineous.)

This proportion, they feel, estimates the frequency of heterozygotes. It does not quite do so, but it does make a start.

Consider for simplicity the case of n loci, each of which has but one recessive allele. Suppose t_j is the frequency of affected persons who owe their disease to locus j. Suppose a proportion Z, independent of j, of affected persons marry unaffected persons and are fertile. If q_j is the frequency of the recessive causing the disease at locus j, among the chromosomes of unaffected persons, who are supposed to mate at random, then

$$4Zt_jq_j(1 - q_j)(1 - q_j^2)^{-1}d$$

will be the frequency of affected by unaffected matings capable of producing an affected, where d is a quantity between zero and one which allows for the fact that, owing to the distribution of sibship sizes, not all families capable of producing both

sorts of offspring will actually do so. Hence, Stevenson and Cheeseman's proportion becomes

$$\frac{4 \sum t_j q_j (1 - q_j)(1 - q_j^2)^{-1} d}{\sum t_j}$$

since Z cancels out, or

$$\frac{2 \sum t_j H_j (1 - I_j)^{-1} d}{\sum t_j}.$$

What one wishes to estimate, however, is either $H = \sum H_j$, or $1 - e^{-H}$ (which equals H when H is small), so that Stevenson and Cheeseman's estimate, by weighting the frequency of carriers at each locus by the frequency of affected due to that locus gives too little weight to the frequency of carriers at every locus, especially to the frequency of carriers at loci which cause the affection rarely. Since loci which contribute but negligibly to the frequency of the disease may contribute materially to the frequency of carriers, the errors by this method can be large, especially if there are many such loci. When there is but one locus and one recessive allele, the method gives a correct result. It should be noted finally that the method does not allow for the possibility that an affected person was heterozygous at some other locus for the disease, in addition to being homozygous at the one to which he owes his affection.

There is no reason, incidentally, to believe that Stevenson and Cheeseman were unaware of these biases; they made it quite clear that they were after but a rough estimate.

It is of interest to obtain, from Stevenson and Cheeseman's data, approximate estimates, by the method presented here, of the mean number of recessives per unaffected and the frequency of carriers.

Stevenson and Cheeseman compute the frequency of congenital deafness of genetic origin as 23×10^{-5} after correcting statistically for the inadvertent inclusion of some cases of non-genetic deafness. These authors assume that congenital deanfess occurring in sibships in which either a parent or another sib has been affected or in which the parents are consanguineous can be supposed to be of genetic origin. Now, among 453 deaf children from unaffected parents, 388 were from non-consanguineous marriages. Of these 388, the authors estimate, by a method we need not review here that 109 are due to non-genetic factors. This leaves 279 genetic cases from non-consanguineous marriages of unaffected by unaffected There are 65 cases from consanguineous, unaffected by unaffected marriages, so that the total number of cases of genetic deafness from marriages involving unaffected parents is 344. There were 38 cases of presumed genetic deafness from marriages involving one or two affected parents. Thus $\frac{344}{344 + 38}$ gives the proportion, among all cases of genetic deafness, of those who come from unaffected parents. By multiplying 23×10^{-5} by $\frac{344}{382}$ we obtain an estimate of the frequency of affected children from unaffected parents; such a quantity estimates I, defined earlier, and equals 2.1×10^{-4}. (Note

that if Stevenson and Cheeseman's series is "contaminated" by the inclusion of some cases of dominant deafness, these will will not disturb our computation. Stevenson and Cheeseman's statistical method for eliminating non-genetic cases will also eliminate cases due to dominant mutations. Of the sample which remains after eliminating the non-genetic cases, we shall be working only with the subsample whose affected come from unaffected parents, thus avoiding cases arising from directly transmitted dominant genes.) The authors quote an estimate of the frequency of first-cousin marriages in the population of Northern Ireland, where they collected their material, as between 0.1 and 0.4 per cent. They estimate the frequency of first-cousin marriages among marriages between unaffected persons producing at least one affected as 9.5 per cent, again, after allowing for the inadvertent inclusion of some cases of non-genetic deafness.

Ideally what one wishes is not the percentage of marriages which are between first cousins in the population as a whole and in the population of unaffected parents producing affected offspring. What one would like instead, as the definitions of c and k given earlier indicate, is the proportion, among all children from unaffected by unaffected marriages, of children from first-cousin marriages and the corresponding proportion among all affected children from such marriages. Obviously, since the condition is rare, one need not worry about the bias in the population figures due to the inclusion of some affected parents. Moreover, if one assumes that the effective fertility of consanguineous matings is approximately the same as the fertility of non-consanguineous ones, then the frequencies of consanguinity among marriages may be substituted for the frequencies of children from consanguineous marriages.

With the formula

$$H = \frac{32\,I\,(k - c)}{c(1 - c)}$$

and with

$$32\,I = 6.7 \times 10^{-3}$$

$$c = 0.001 \text{ or } 0.004$$

$$k = 0.095$$

we compute the following values:

c	H	F	R	G, %
0.001	0.630	0.468	1506	99.9
0.004	0.153	0.142	365	99.7

where F = frequency of genetic carriers, or $1 - e^{-H}$.

We can now contrast (table 1) the average number of recessives per person computed by

1) employing the frequency of the disease among the children of unaffected non-consanguineous parents, call it b^2, and evaluating $2b(1 - b)$;

2) the method of Stevenson and Cheeseman (1956) described earlier;

3) the method proposed in the present paper.

TABLE 1. THE FREQUENCY OF CARRIERS OF THE RECESSIVE GENES RESPONSIBILE FOR DEAFNESS, AS ESTIMATED BY THREE DIFFERENT METHODS

Method	Mean number of genetic carriers
1. Hardy-Weinberg	0.026
2. Stevenson and Cheeseman, 1956	0.114
3. Present method	0.630 to 0.153*

* Depending on whether c is taken as 0.001 or 0.004 respectively. (The rather wide range created by these two values is not a characteristic of the method itself; it arises from the fact that Stevenson and Cheeseman were obliged to specify the population consanguinity rate as an unknown value falling probably between the two values used.)

The first method (Hardy-Weinberg) assumes all the probability is concentrated at a single locus with a single recessive allele. The second method also makes this assumption but might work adequately for the order of magnitude of the frequency of carriers when the probability is concentrated over a small number of loci and alleles. The third method does not constrain the number of alleles or loci.

Stevenson and Cheeseman give the frequency of genetic deafness among the children of non-cnsanguineous marriages as 20×10^{-5}. Of 314 non-consanguineous cases given in their table IV, 279, after eliminating the non-genetic cases they estimate to be present, come from unaffected by unaffected marriages.

Thus $b^2 = \frac{279}{314} \times 20 \times 10^{-5} = 1.8 \times 10^{-4}$.

The fact that Stevenson and Cheeseman's method gives a result of the same order of magnitude as the present method may be taken as evidence supporting the view that most of the probability attached to the alleles and loci determining this condition is concentrated in a few alleles and at a few loci.

SUMMARY

Consider a rare disease caused solely by a double dose of any one of several recessive alleles at any one of n different loci. At locus 1_j there are (A_{ij}) dominant alleles such that i varies from 1 to f_j, and (a_{ij}) recessive alleles such that i varies from 1 to m_j. Suppose p_{ij} is the frequency of A_{ij} and q_{ij} is the frequency of a_{ij}.

If

c = the proportion, among all children in the population of unaffected parents, of children who come from first-cousin marriages,

k = the proportion, among all affected children of unaffected parents, of children who come from first-cousin marriages,

I = the frequency of the disease among all children of unaffected parents, and if

H = the average number of recessive genes for the disease, carried by unaffected persons, per unaffected person, and

F = the proportion of unaffected people who carry at least one such recessive, then

$$H = \frac{32\, I\,(k - c)}{c(1 - c)} \text{ and } \mathcal{F} = 1 - e^{-H},$$

free of the rank, order, and elements, of the matrices $[p_{ij}]$ and $[q_{ij}]$. It is immaterial whether persons of genotype of $a_{ij}a_{ij}$ show the disease, and are, therefore, counted as affected, or do not show the disease and therefore contribute, in the amount of twice their frequency, to the average number of recessives for the disease per unaffected person.

The assumptions necessary for the derivation are set out. They are no more stringent than those usually employed when the Hardy-Weinberg relation is used to estimate the frequency of carriers of a single recessive gene at a single locus from the frequency of recessives. Random mating is assumed only among unaffected.

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The Mathematical Relations Among Plural Births

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In 1895 Hellin reported that the ratio of single births to twin births was almost the same as that of twins to triplets and triplets to quadruplets. The relation was discovered independently by Edgar (1916) and by Zeleny (1921), but it is generally known as Hellin's law. Many writers have shown that Hellin's law fails to fit observation in a statistical sense, but its usefulness as a rule of thumb cannot be denied. Actually, the findings to be reported here suggest that the agreement of Hellin's law with birth statistics is not entirely coincidental, and that it fits the data partly because of underlying truth and partly because its two major defects tend to cancel each other.

Hellin's law was derived without reference to the zygosity classification of multiple births. The existence of two kinds of twins precludes any meaningful treatment of twin frequency as a single datum, and Jenkins (1929) showed that the distribution of sex-concordance in higher orders of plural birth eliminates any simple explanation of Hellin's findings. Jenkins divided the frequency of twins into its two components, monozygotic (here designated by a) and dizygotic (b), and expanded the resulting binomial to obtain the frequencies of zygosity types in triplets, a^2, $2ab$ and b^2. The *a priori* relation of zygosity to sex-concordance in twins and triplets had been recognized by Bertillon (1874): the probability that a second zygote will have the same sex as the first is $\frac{1}{2}$; the probability that second and third zygotes will both have the same sex as the first is $\frac{1}{4}$. Jenkins combined the binomial expansion with Bertillon's triplet rule and found very poor agreement with birth statistics. This discrepancy is illustrated in table 1 with recent data for U. S. Whites, in which the relative[3] twin frequencies were .3757 for MZ (a) and .6243 for DZ (b). This comparison of observed with expected yields a chi-square of 22. In an attempt to reconcile the observations with Hellin's law, Jenkins and Gwin (1940) applied fractional coefficients to all three terms of the expansion.

It appears that Hellin's law might logically apply to ovulation. If extra ovulation occurs at random once in every 156 times (the frequency of DZ twins among U. S. White births, 1952-1954), two extra ovulations would coincide once in every 156 squared, three once in every 156 cubed. This assumes that at all stages in the genesis of multiple embryos by extra ovulation the probability of another ovulation is constant. But for *zygotic division* it would be more logical to assume that the probability of division *per gestation* depends upon the number of embryos. Thus the simplest hypothesis, mathematically, is that *at any stage in the genesis of multiple embryos the*

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[3] Except in computation of the expected *total* frequency of triplets or quadruplets, relative frequencies of MZ and DZ twins among twin births give the same results as the respective frequencies among all births. The relative values are a little more convenient to work with, and will be used throughout this paper when applicable.

TABLE 1. ZYGOSITY AND SEX-CONCORDANCE IN TRIPLETS AS CALCULATED FROM THE BINOMIAL EXPANSION OF HELLIN'S LAW

		One-egg	Two-egg	Three-egg	Total
General Formulas	Zygosity Types	a^2	2ab	b^2	1
	Probability of Sex-concordance	1	$\frac{1}{2}$	$\frac{1}{4}$	
U. S. Whites Expected (for 973 triplets born 1952–1954)	Zygosity Types	137	457	379	973
	Frequency of Sex-concordance	137	228.5	95	460.5
U. S. Whites Observed	Frequency of Sex-concordance				533

probability that a division will occur is the individual probability of division multiplied by the number of embryos. Thus if the probability of division of one embryo is one in 260 (MZ twins among U. S. White births, 1952–1954), the probability for division of either of two embryos would be one in 130, and that for any of three embryos would be one in 86.7. This will be referred to as the hypothesis of proportional probability of embryonic division. The underlying principle was assumed by Das (1953, 1955) in the derivation of his triplet formulas.

The hypothesis can be expressed graphically and algebraically. Figure 1 diagrams the processes of embryo multiplication. Twins may result from the release of two ova or from primary division of one ovum. The probabilities of these events among all pregnancies are represented by b and a, respectively, and should be nearly equivalent to the frequencies of the two types of twins at birth. One-egg triplets are derived from one-egg twin embryos by secondary division of either of the two products of the first division. The probability of secondary division in such a half-embryo may be taken as a'. Since there are two such embryos, the ratio of one-egg triplets to one-egg twins should be $2a'$. Similarly, two-egg twin embryos can give rise to triplets by *primary* division of either, with a frequency of $2a$. A small proportion, b', of double ovulations will be accompanied by an additional ovulation, resulting in three-egg triplets.

One-egg quadruplets may be derived from one-egg triplet embryos in two ways. There are two embryos that could undergo a tertiary division, each with probability a'', and one embryo that could undergo a secondary division with probability a'. Jenkins (1929) noted this, but confused monozygotic and tetrazygotic sets and overlooked the unequal probabilities of the two monozygotic types. The derivation of two-egg quadruplets beyond the twin stage is exactly analogous to that of one-egg sets, but the divisions are secondary and primary, respectively, instead of tertiary and secondary. Three-egg quadruplets may occur by primary division of any of the three embryos. Four-egg quadruplets will be related to three-egg triplets by the ratio, b'', the frequency of a fourth ovulation following three. In similar fashion one can derive the types of quintuplets and higher orders of birth.

In order to simplify the algebraic expressions it is very helpful to assume, as a first approximation, that a, a', a'', etc., are all equal, and similarly for b, b', b'', etc. Then

GENESIS OF MULTIPLE EMBRYOS

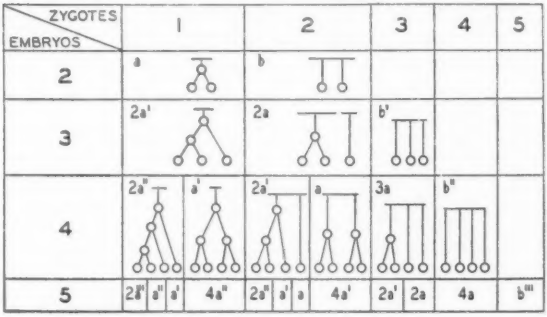

FIG. 1

TABLE 2. APPROXIMATE EXPECTATION OF PLURAL EMBRYO FREQUENCIES BASED ON THE HYPOTHESIS OF PROPORTIONAL EMBRYONIC DIVISION

Embryos	Zygotes				
	1	2	3	4	5
2	a	b			
3	$2a^2$	2ab	b^2		
4	$6a^3$	$6a^2b$	$3ab^2$	b^3	
5	$24a^4$	$24a^3b$	$12a^2b^2$	$4ab^3$	b^4

the frequency of each zygosity type can be derived from the one above it by a factor of a multiplied by the number of embryos that could divide. Under these assumptions, monozygotic plural births would have a frequency of a for twins, $2a^2$ for triplets, $6a^3$ for quadruplets, and $24a^4$ for quintuplets.

Table 2 shows the results of this simplification, together with other simplifications to be discussed below. If n is the number of embryos, then $(n - 1)$ appears in each term both as the sum of the exponents of a and b and as the ratio of the coefficient to that of the term above it. The terms on the right, plural births resulting only from multiple ovulation, are successive powers of b without any coefficients, relics of Hellin's law.

The simplifications upon which table 2 is based require some discussion. Chief among these is the assumption of equality among a, a', etc., and among b, b', etc. It seems likely that primary division of an embryo should have the same probability regardless of the number of other embryos in the uterus, and this is true for all secondary divisions and all tertiary divisions. It is not so safe to assume that all these different orders of division have one common probability. The probability might be greater for secondary and tertiary divisions if each division occurred selectively in those embryos with the greatest tendency to divide, but this trend might be compensated or reversed by diminishing size of the divided embryos and by physiological development with passage of time. Likewise, successive probabilities of multiple ovulation might either increase or decrease.

A second important simplification in table 2 is the omission of all factors in the form $(1 - a)$ or $(1 - b)$. Table 2 applies, strictly, only to stages of embryo multi-

TABLE 3. EXACT FREQUENCIES OF GESTATIONS BY PLURALITY AND ZYGOSITY AFTER COMPLETION OF EMBRYO MULTIPLICATION

Embryos	Zygotes		
	1	2	3
1	$(1 - a)(1 - b)$		
2	$a(1 - b)(1 - a')^2$	$b(1 - b')(1 - a)^2$	
3	$2aa'(1 - b)(1 - a')(1 - a'')^2$	$2ab(1 - b')(1 - a)(1 - a')^2$	$bb'(1 - b'')(1 - a)^3$

plication and not to plural gestations at term. All multiple pregnancies have passed through the one-egg stage, and were removed from the total of single *births* either by division of the embryo, with frequency a, or by the addition of another egg, with frequency b. The probability of a gestation remaining at the one-embryo stage is therefore $(1 - a)(1 - b)$. Table 3 includes in every term a correction for those gestations that go on to a higher order of plurality, so that each term represents the expected relative frequency at birth. From the table it is clear that the parameters a and b, which represent probabilities of embryonic division and extra ovulation, would be underestimated by the frequencies of MZ and DZ twins at birth even if there were no fetal losses. Better estimates would result if these frequencies were divided by $(1 - b)(1 - a)^2$, in which as a first approximation a and b are the frequencies of MZ and DZ twins among all births.

If the first of the above approximations is accepted, then the second does not affect the relative frequencies of zygosity classes, but only the total numbers in each order of birth. The estimate of triplets from table 2 would be too low by $(1 - a)(1 - b)$, and that of quadruplets by $(1 - a)^2(1 - b)^2$. For precise estimation of the theoretical total of plural births, an adequate adjustment is provided by the use of MZ and DZ twin frequencies in these corrections. For maternal ages 35 to 39, where twin births are at a maximum, the data of Waterhouse (1950) yield corrections that increase the estimate of triplets by 2.1 per cent and that of quadruplets by 3.5 per cent. In population data the error is trivial.

Another assumption throughout this analysis is that male and female zygotes or embryos have equal twinning tendencies and similar survival to birth. Survival of the sexes is of course not equal, and equality of the twinning tendency has often been questioned. Das (1953, 1955) has recently explored some of the consequences of a difference in twinning tendency, but his otherwise precise formulas did not allow for the very important possibility of interaction between plural gestation and differential survival of the sexes. Actually, the deviation from the normal sex ratio is downward in twins and triplets, but upward in quadruplets (Hamlett, 1935) and quintuplets (MacArthur and Ford, 1937). At this stage of knowledge, the complication and speculation introduced into the formulas by adjustment for sex ratio would not seem to be warranted by the very small possible gain in precision.

In its simplified formulation, the hypothesis can be tested both against the relative proportions of sex-concordance types and against the absolute numbers of plural births in available birth statistics.

A prediction of sex-concordance requires a hypothesis about the relation, at each order of plural birth, between zygosity types and sex-concordance. In the case of triplets this is simple. It was recognized by Bertillon (1874) and Weinberg (1902),

from elementary probability considerations, that same-sex sets should comprise half of all dizygotic triplets and a quarter of all trizygotic triplets. Half of the dizygotics and three-quarters of the trizygotics should be of mixed sex. For quadruplets and higher orders the calculation becomes more complicated, because mixed sets are of two or more types (e.g., 3:1 and 2:2) and because division may occur either in a product of the preceding division or in one of the other embryos. Table 2 implies that division occurs at random (i.e., with equal probability) in single and divided embryos. This is not inconsistent with our present knowledge of twins, for in other respects both types of embryo manifest similar developmental potentialities. Computed on this basis, table 4 shows the expected relative frequencies of sex-concordance types within each zygosity class. Jenkins (1929) attempted to formulate such a rule for quadruplets, but he assumed that the two dizygotic types of quadruplets would be equally frequent.

Application of the fractions in table 4 to the zygosity-class frequencies computed from table 2 yields estimates of sex-concordance classes that can be summed for each order of multiple birth. Since total numbers of sets are not here in question, relative frequencies of MZ and DZ twins can be used instead of absolute frequencies. Table 5

TABLE 4. PROBABILITIES OF SEX-CONCORDANCE TYPES WITHIN EACH ZYGOSITY TYPE IF EMBRYONIC DIVISION AND EXTRA OVULATION COMBINE AT RANDOM

Embryos	Sex	Zygotes				
		1	2	3	4	5
2	Same	1	$\frac{1}{2}$			
	Opp.	0	$\frac{1}{2}$			
3	Same	1	$\frac{1}{2}$	$\frac{1}{4}$		
	Mixed	0	$\frac{1}{2}$	$\frac{3}{4}$		
4	Same	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{8}$	
	3:1	0	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{2}$	
	2:2	0	$\frac{1}{6}$	$\frac{1}{4}$	$\frac{3}{8}$	
5	Same	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$
	4:1	0	$\frac{1}{4}$	$\frac{3}{8}$	$\frac{3}{8}$	$\frac{5}{16}$
	3:2	0	$\frac{1}{4}$	$\frac{3}{8}$	$\frac{1}{2}$	$\frac{5}{8}$

TABLE 5. PREDICTION OF SEX-CONCORDANCE IN PLURAL BIRTHS. PRESENT HYPOTHESIS (1) COMPARED WITH BINOMIAL EXPANSION OF HELLIN'S LAW (2). (HAMLETT)

Triplets	Same-sex	Mixed		Chi²	p
Observed	1437	1346			
Expected (1)	1398	1385		2.2	>.10
Expected (2)	1242	1541		55.3	<.01
Quadruplets	Same-sex	1:3	2:2		
Observed	20	12	8		
Expected (1)	17.0	14.7	8.4	1.0	>.50
Expected (2)	11.9	17.8	10.3	8.1	<.05
Quintuplets	Same-sex	1:4	2:3		
Observed	16	9	15		
Expected (1)	15.7	11.1	13.2	0.6	>.50
Expected (2)	8.0	13.8	18.2	10.2	<.01

compares expected and observed frequencies of sex-concordance classes in triplets and quadruplets for U. S. White births from 1915 to 1930 (data of Hamlett, 1935), and in quintuplets collected from the literature by MacArthur and Ford (1937). Since the population source of the quintuplets cannot be identified, but is probably mainly Caucasian, values of a and b for this calculation were based on the twin data of Hamlett, $a = .336$ and $b = .664$. In all three tests the proposed formulas satisfactorily predict the frequencies observed, while the simple binomial expansion of Hellin's law, shown for comparison, is significantly in error.

A more crucial test is provided by populations with diverse frequencies of dizygotic twinning. In table 6, triplets of three populations are compared with the predictions of sex-concordance given by the proposed formula. The first row, U. S. Whites for 1952–1954 ($a = .3757$, $b = .6243$), is expected to fit about as well as Hamlett's older data, and it fits somewhat better, with a chi-square of only 0.3. The second row shows U. S. Negroes, who have a higher frequency of DZ twinning ($a = .2783$, $b = .7217$). The last row shows Tokyo Japanese (data from Inouye, 1956), in whom the frequency of dizygotic twinning is very low ($a = .644$, $b = .356$). The predictions prove accurate for all three populations. It is however noteworthy that, except for the Japanese, all examples in tables 5 and 6 show a non-significant excess of same-sex sets.

The hypothesis does not appear to yield such accurate predictions of the total numbers of triplets and quadruplets. As Hellin's law has always emphasized, the ratio between successive orders of reported plural births is nearly constant, but the hypothesis of proportional probability of division implies an increasing ratio. The excess in table 2 over Hellin's law is a^2 for triplets and $5a^3 + 3a^2b$ for quadruplets. Necessarily, therefore, the resulting estimates exceed *reported* plural births. This is apparent in table 7, whether data are based on total reported births or on live births only. However, the tabulation of plural stillbirths in *Vital Statistics of the United States* (National Office of Vital Statistics) is evidently incomplete, probably because an estimated gestation age below 20 weeks takes reports out of the stillbirth category. For example, in the eight years 1947-1954, 23 sets of quadruplets were reported with all born alive, four with one stillborn, and none with two or more stillborn. This stillbirth rate is lower than that reported in triplets. The close agreement with expectation in the Japanese data may tend to indicate the effect of more complete reporting of stillbirths, or it may be entirely due to the small sample size.

In addition to the algebraic simplifications already discussed, the calculations represented in tables 5, 6 and 7 contain two major sources of inaccuracy. First, they are based on pooled data for all maternal ages. In order to evaluate the magnitude of

TABLE 6. SEX-CONCORDANCE AMONG TRIPLET BIRTHS IN THREE POPULATIONS

Population	MZ/DZ Ratio		Same-sex	Mixed	Chi²
U. S. Whites	.60	Obs.	533	440	
1952–1954		Exp.	524	449	0.3
U. S. Negroes	.39	Obs.	118	125	
1952–1954		Exp.	110	133	1.1
Tokyo Japanese	1.81	Obs.	15	6	
1950–1951		Exp.	16.2	4.8	0.4

TABLE 7. TOTAL FREQUENCY OF TRIPLETS AND QUADRUPLETS COMPARED WITH THE HYPOTHESIS

		Observed	Expected	Ratio
U. S. White Triplets	1952–1954			
total:		973	1234	.79
live births only:		822	1062	.77
U. S. White Quadruplets	1947–1954			
total:		27	43	.63
live births only:		23	34	.68
U. S. Negro Triplets	1952–1954			
total:		243	341	.71
live births only:		187	272	.69
Tokyo Japanese Triplets	1950–1951			
total:		21	21.6	.97
live births only:		5	11.8	.42

Twin frequencies used in these calculations were as follows: White, total, a = .003853, b = .006403; live births only, a = .003447, b = .006196. Negro, total, a = .003903, b = .01012; live births only, a = .003420, b = .009330. Japanese, total, a = .00451, b = .00249: live births only, a = .00345, b = .00196.

this error, the New York State data of Yerushalmy and Sheerar (1940) were analyzed in 5-year maternal age groups. The age-specific data gave a lower prediction of same-sex sets than did the pooled data. The difference was less than three per cent of the same-sex sets, but in a direction that would increase the discrepancies in tables 5 and 6. These authors gave no triplet data for comparison with the predictions, and differences among the populations would vitiate any correction of our other estimates on the basis of the New York statistics.

Finally, many pregnancy terminations are not reported or even reportable. There is always some error in the assumption that reported plural births are representative of all multiple gestations, whether in sex-concordance, in zygosity, or in plurality. The data for recent U. S. births cited here were taken from *Vital Statistics of the United States*, which lists some incomplete plural birth reports. For the present calculations these incomplete reports were assumed to involve stillbirths and were added *pro rata* to the appropriate categories of race and sex-concordance. This appeared to be better than omitting them altogether, although they probably have a different distribution than fully reported stillbirths. Unreported fetal losses may be still less representative and are certainly more numerous (Guttmacher, 1953). Preferential survival of polyzygotic sets or more careful reporting of same-sex sets of stillbirths, for example, might distort the true proportions significantly.

To the extent that these distortions occur in twins, they would be incorporated and hence compensated in predictions of the higher pluralities. This "automatic" correction will be further discussed below.

DISCUSSION

The hypothesis of proportional probability of embryonic division as represented in table 3 may be viewed tentatively as a complete description of the genesis of plural embryos, within any homogeneous group of mothers. This requires, however, that the large deficiency of U. S. triplets and quadruplets shown in table 7 be explained mainly

in terms of unreported intrauterine mortality. Comparison with the Japanese data may shed some light on the problem. In Tokyo, stillbirths were reported for 8 per cent of single births, for 29 per cent of twin pregnancies and for 76 per cent of triplet pregnancies. The corresponding stillbirth rates for U. S. Whites are 1.6 per cent, 6 per cent and 18 percent; for both populations the stillbirths are approximately in the ratio of 1:4:10. While stillbirth rates are undoubtedly higher in Japan, it seems likely that part of this difference is due to more complete reporting in Tokyo, and the low stillbirth rate already cited for U. S. quadruplets supports this belief.

Since stillbirths are much more frequent in twins than in single births, live birth statistics show lower relative frequencies of twins than do total birth data. The decrement is magnified in the resulting estimate of triplets. Consequently, if stillbirths are uniformly underreported, even total births of singletons and twins will give a low estimate of total triplet births, but this deficiency may be matched or exceeded by high mortality and underreporting in triplets. When unrecognized or unreported intrauterine deaths are considered in addition to reported stillbirths, it appears that the calculated estimate of triplets may always be low, and that any close correspondence between this automatic correction and the actual underreporting of triplet gestations, as apparently occurred in the Japanese data, must be mainly coincidental.

In short, much more information will be needed about fetal losses before total plural births can be used either to refute or to confirm our hypothesis. Nevertheless, close agreement of the hypothesis with sex-concordance data for three pluralities and three (or four) populations would seem to offer strong support. If so, some of the consequences of the hypothesis deserve exploration.

By comparison with predictions from twin data (table 7) it appears that the proportion of U. S. White triplets lost or reduced to a lower order of birth between conception and reporting is approximately 20 per cent. For Negroes the loss is 30 per cent and for White quadruplets it is nearly 40 per cent. These figures are minimal estimates of unreported losses in triplet and quadruplet pregnancies if the hypothesis is valid. The losses may be considerably greater if unreported terminations are much higher in twin than in single gestations. However, the close conformity of sex-concordance types to expectation implies that, whatever their nature may be, the excess losses in the highest orders of multiple birth depend on the number of fetuses present and are almost independent of zygosity types.

Examination of table 2 reveals that, in each order of plural birth, the terms for monozygotic and dizygotic sets, respectively, are in the ratio $a:b$. In fact, this follows logically from the assumptions, since these two zygosity types are derived from the respective types of twin embryos by exactly parallel processes of division, and therefore have initial relative probabilities of a and b. If the MZ/DZ ratio is found to change in successive orders of multiple birth, it will afford a means of evaluating the respective probabilities of division: primary, secondary, tertiary, etc. In that case, the ratio would be virtually a'/b for triplets, giving a direct measure of a'. If the change in probability of division is regular, that is, if the values of a, a' and a'' form a geometric progression, then the MZ/DZ ratio should be $(a/b)x$ in triplets and $(a/b)x^2$ in quadruplets, where x is the ratio of a' to a. Both a and b can be accurately estimated from twin data, and no zygosity class in figure 1 except trizygotic quintuplets com-

bines a', a'', b' or b'' with unknown forms of the other parameter. Although rather large numbers of plural births would have to be classified by zygosity to reveal differences among a, a' and a'', or among b, b' and b'', the efficient utilization of such zygosity data to this end should be easy.

On the other hand, the agreement between observation and hypothesis in tables 5 and 6 suggests that a, a' and a'' are nearly equal, and hence that the MZ/DZ ratio is nearly the same for all orders of plural birth. This should be very useful for the solution of zygosity problems involving triplets, quadruplets or quintuplets. Newman (1940) assumed that nearly all same-sex sets of quadruplets and quintuplets were derived from single zygotes, but according to the present formulas less than half of such sets are monozygotic in the U. S. population. When blood factors are alike in a same-sex set, three or more zygotes can usually be excluded by probability calculations, and the problem reduces to that found in twins, a decision between one zygote and two. Under our hypothesis, the relative probabilities in this situation are apparently the same as those for twins.

It should be recognized that rather large errors can be introduced into zygosity diagnoses by disregard of the effect of maternal age on the frequency of extra ovulation. This figure is important in computations of the relative probability that twins are monozygotic either by the method of Sutton, Clark and Schull (1955) or by that of Smith and Penrose (1955). The MZ/DZ ratio varies as much among mothers of different age-groups as among races. According to Waterhouse (1950) it ranges in the British population from .28 in mothers 35 to 40 to four times this figure in the youngest mothers. Maternal age is easily ascertained for most cases of plural birth, so that there is generally no excuse for basing zygosity computations on the average MZ/DZ ratio for the population. The necessary information has been published for several Caucasian populations, and it is to be hoped that collection and publication of data on plural births by maternal age will become a more general practice.

The effects of parity on twinning are at present neither sufficiently striking nor sufficiently well documented to be taken into account in zygosity calculations.

SUMMARY

Hellin's law can be translated into powers of a binomial based on the population frequencies of the two types of twins. The terms of this binomial, expanded to any order, give expected frequencies of all zygosity classes in the respective order of multiple birth. These predictions prove incompatible with the observed distribution of sex in triplets, quadruplets and quintuplets.

Good agreement, however, is obtained on a hypothesis of proportional probability of embryonic division based on the additivity of independent probabilities. According to this, any kind of plural birth should be numerically related to the next higher order derived from the same number of zygotes by the probability of embryonic division multiplied by the number of embryos capable of dividing. Each order of plural birth adds a new term representing the maximum number of zygotes: trizygotic triplets, tetrazygotic quadruplets and pentazygotic quintuplets and these terms, starting with the frequency of dizygotic twins among all births, form a geometric series like Hellin's law.

Sex-concordance types can be predicted for each zygosity class. The sums of these, within any order of plural birth, can be compared with observed sex-concordance types. When this is done, excellent agreement is obtained for triplets of three different races and, in Whites, for quadruplets and quintuplets also. The total numbers of triplets and quadruplets predicted, however, are considerably above those given by available U. S. statistics. This suggests relatively high prenatal mortality, nearly independent of zygosity, in the higher orders of plural birth.

The proposed formulas define a number of biological parameters so that these should eventually be measurable. The monozygotic-dizygotic ratio would seem to be nearly the same for all orders of plural birth, but the dependence of this ratio on maternal age should be recognized in every zygosity problem.

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Chances of Disproof of False Claims of Parent-Child Relationship[1]

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GENETIC METHODS HAVE FOUND a new application in tests of claims of derivative citizenship. Such claims, mostly by Chinese who claim to be the children of Chinese fathers who are American citizens, have multiplied enormously in recent years, amounting to 7000 in a three year period (Sussman 1956). When blood group tests were introduced by the Immigration and Naturalization Service it was shown that 40 percent of the claims were false, which suggested "the existence of an immense 'immigration ring' whose motivation and scope could only be guessed." (Or perhaps merely that a number of Chinese prefer capitalism to communism?) From the per cent of the claims which were shown to be false, Sussman attempted to compute the proportion which must have been actually false, but was able to obtain an approximate answer only, because of the lack of figures for the probability of disproving a false claim of parent-child relationship by some of the blood group systems available.

Cotterman (1951) has derived general formulas for the chances of disproving false claims of relationship by two-gene allele systems, and it is simple, though tedious, to calculate the numerical probabilities for more complicated systems. Fisher (1951) has proposed a convenient way of laying out the computations, and derived the chances for the English population, using the MNS blood group system. The results of similar calculations for Chinese populations for the 5 blood group systems for which Chinese data are available are presented in table 1. For the sake of comparison, and because the results may be of interest to members of the legal profession confronted in this country with cases of disputed claims of parent-child relationship, a similar table for the white population of the United States is presented (table 2). In some cases a false claim of relationship can be disproved even if only one alleged parent is tested, and the chances of doing this are also included in tables 1 and 2.

In presenting tables relative to the related but distinct problem of disproving paternity, it has been found convenient to present probabilities based on two different assumed levels of testing, since all of the desired antisera are not always available (Race and Sanger 1954, Boyd 1954). I have accordingly done this in preparing tables 1 and 2. The assumed second level of testing is the same as the first in the case of the ABO, Lutheran and secreting systems, being tested with anti-A and anti-B in the first, with anti-Lu^a in the second, and testing for secretion or non-secretion in the

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TABLE 1. CHANCES OF DISPROVING FALSE CLAIMS OF PARENT-CHILD RELATIONSHIP BY VARIOUS BLOOD GROUP SYSTEMS. (CHINESE POPULATION)

System	Exclusion by Each System (first level)	Combined Exclusion (first level)	Exclusion by Each System (second level)	Combined Exclusion (second level)
		2 PARENTS TESTED		
ABO	0.3301	0.3301	0.3301	0.3301
MNS	0.2771	0.5157	0.3736	0.5803
Rh	0.2678	0.6454	0.2747	0.6956
Duffy	0.0312	0.6565	0.1424	0.7390
Kidd	0.1186	0.6972	0.2578	0.8063
Kell	0		0	
Lutheran	?		?	
Secreting	?		?	
		1 PARENT TESTED		
ABO	0.0419	0.0419	0.0419	0.0419
MNS	0.1203	0.1571	0.1203	0.1571
Rh	0.0644	0.2114	0.0757	0.2209
Duffy	0		0.0158	0.2332
Kidd	0		0.0916	0.3034
Kell	0		0	
Lutheran	0		?	
Secreting	0		?	

third. In the other systems the second level of testing implies the use of one more antiserum, such as anti-s, anti-e, anti-Fy^b, anti-Jk^b, and anti-k.

The ABO and MN blood group frequencies for the Chinese have been taken from Sussman's series of 706, the Rh results from the series of 250 Southern Chinese of Simmons *et al.* (1950), and the other values from the series of 103 of Miller *et al.* (1951). For white Americans I have used my own ABO data from Boston (Boyd 1939) and for the other data various large series summarized in Mourant (1954), using English data where no American series existed. Sussman's Chinese Rh results are somewhat different from those of Simmons *et al.*, as the former finds gene *cde* present, though rare, and *CDE* absent, whereas with the latter this situation is reversed. This makes however very little difference in the calculated chances of disproving false claims of relationship; the value for tests with four sera is from the former results 0.2638 and from the latter 0.2678. No data on the Lutheran blood groups for the Chinese seem available and the only estimate of the frequency of the secreting gene is one by the possibly uncertain method of reasoning from the Lewis blood group frequencies (Miller *et al.* 1951, Mourant 1954).

A comparison of these tables with similar tables for the probabilities of establishing non-paternity (Race and Sanger 1954, Boyd 1954) shows that the probabilities of disproving false claims of relationship are consistently greater. The combined probabilities for the Chinese, using five blood group systems at the second level of testing, would enable false claims to be disproved in over 80 per cent of the cases.

It is not yet known what the blood group frequencies are in the interior of China. If the variation is great, than the chances of detection of false claims when the persons

TABLE 2. CHANCES OF DISPROVING FALSE CLAIMS OF PARENT-CHILD RELATIONSHIP BY VARIOUS BLOOD GROUP SYSTEMS. (WHITE AMERICAN POPULATION)

System	Exclusion by Each System (first level)	Combined Exclusion (first level)	Exclusion by Each System (second level)	Combined Exclusion (second level)
	2 PARENTS TESTED			
ABO	0.2866	0.2866	0.2866	0.2866
MNS	0.2811	0.4872	0.3568	0.5411
Rh	0.4070	0.6959	0.4225	0.7350
Duffy	0.0779	0.7196	0.2765	0.8083
Kidd	0.0416	0.7312	0.2811	0.8621
Kell	0.0657	0.7489	0.0676	0.8715
Lutheran	0.0537	0.7624	0.0537	0.8784
Secreting	0.0265	0.7687	0.0265	0.8816
	1 PARENT TESTED			
ABO	0.0352	0.0352	0.0352	0.0352
MNS	0.1224	0.1533	0.1224	0.1563
Rh	0.1368	0.2691	0.1568	0.2860
Duffy	0		0.1175	0.3699
Kidd	0		0.1247	0.4485
Kell	0		0.0001	0.4486
Lutheran	0		0	
Secreting	0		0	

come from the same village, might be slightly different from those given here; I do not believe the difference would be great.

We may now attempt to answer the question posed by Sussman; of the series of claims, 40 per cent of which were disproved, how many were in fact false? These cases were evidently tested using the ABO, MN and Rh systems at the first level of testing, testing both parents, so the probability of disproving a false claim is 0.6454. The percentage of false claims in the series was therefore 40/0.6454, or about 62 per cent, less than the 80 per cent estimated by Sussman, but still astonishingly high.

It is perhaps worth mentioning that whereas the chances of establishing non-paternity by the more complex blood group systems may be found with only slight error by assuming the various connected systems (e.g. MN, Ss; Cc, Dd, Ee) to be independent (Boyd 1955), attempts to use this simplification in the present problem give results that are considerably too high (e.g. 0.3463 instead of 0.2638 for the Rh system).

SUMMARY

Tables are presented for the chances of disproving false claims of parent-child relationship by blood grouping tests, for Chinese and white American populations.

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Monilethrix: Report of a Family With Special Reference to Some Problems Concerning Inheritance

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MONILETHRIX IS AN UNCOMMON DISEASE first described in 1879 by W. G. Smith of Dublin and by Luce in France. It is characterized by a peculiar beading of the hair and an associated keratosis follicularis. The onset is gradual, being first noticed a few weeks or months after birth when the normal hair is replaced by moniliform hair. In a few of the reported cases the onset was much later. The first signs of disease were discovered in the patient described by Ruggles (1900) at 3 to 5 years of age, in Francis's patient at 15 years, and in the patient of Gilchrist (1898) at 17 years. In the family reported by Hanhart (1955), where the disease is thought to be due to a recessive gene, it seems to have started in one member relatively late, probably in his early twenties.

The hair may be abnormal over the entire scalp, but more often only a portion is affected, usually the occiput. In some cases the hair of the eyelashes, eyebrows, axilla, pubis, trunk and extremities may be altered in the same way. When the entire scalp is affected the patient may be totally bald or may have a sparse covering of short broken hair. When monilethrix is local the more normal hair is frequently short and thin.

Keratosis follicularis may develop before or shortly after the appearance of abnormal hair. It may involve the scalp, neck and limbs, and does not necessarily coincide with parts covered by moniliform hair.

The abnormal hairs usually show constrictions at regular intervals, but some are atrophic over their whole length. They are very brittle and may break off at a constriction after reaching a length of about one to three centimeters. Microscopically the spindle-shaped parts of the hair are normal, but at the constrictions the cortex is reduced and the medulla usually absent (figure 1). The keratosis is not the cause of the beading, as moniliform hairs may grow where there is no keratosis and the hairs are abnormal before they emerge from the follicles.

Affected individuals are usually healthy and of good physique. A few associated defects have been described (Sabouraud, 1892; Rosenthal and Speiregen, 1928; Racz and Turi, 1954), but at least some of these are probably coincidental.

Cockayne (1933) tabulated the cases then available and concluded that the condition was due to a dominant gene without sex limitation. In some reported families penetrance of the gene appears to have been incomplete, but it should be noted that none of the apparent carriers were thoroughly examined by the original author. Two alleged carriers occurred in our family, and we shall discuss the question of incomplete penetrance further.

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FIG. 1 SOME TYPICAL MONILIFORM HAIRS (CASE IV, 2)

FAMILY RECORD

This family (figure 2) was examined in 1954 and again in 1956. All living members were seen and hair samples were studied microscopically in most cases. Three members of the family had died at the time of examination. Reliable information and photographs enabled us to reach a diagnosis of monilethrix for two of these. The status of the third deceased member (II-1) remains doubtful, but she is classed as normal by relatives and by photograph. As small lesions easily pass unnoticed and hair samples have not been studied, the value of information supplied by relatives is questionable.

I-1: Female, age 79 years. The head is covered with short dark greying hair. No information could be obtained about keratosis because of lack of cooperation. A hair sample showed typical beaded hairs. Diagnosis: monilethrix.

II-1: Female, died at age 44.5 years, cause unknown. According to photographs and relatives her hair was completely normal and of dark color. Diagnosis: doubtful.

II-2: Female, paternal grandmother of the propositus, killed during World War II at age 49 years. According to photographs and reports of relatives her head was covered by short dark hair with the occiput particularly affected. No information about keratosis. Diagnosis: monilethrix.

II-3: Male, died of peritonitis at age 46 years. According to reliable information his scalp was sparsely covered by short dark hair that easily broke off during the act of brushing, with most severe involvement at the occiput. No information about keratosis. Diagnosis: monilethrix.

II-4: Male, age 54 years. The scalp is covered by dark greying hair that is dry and short, especially over the occiput where keratosis occurs. No other region of

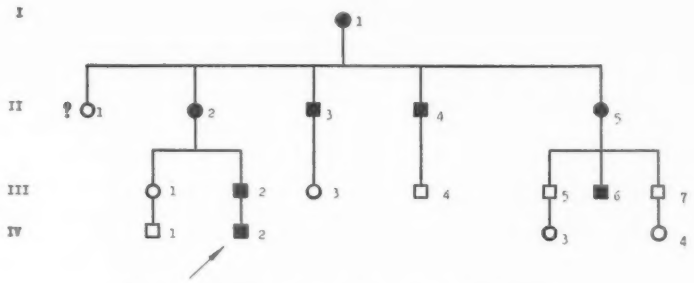

FIG. 2 PEDIGREE OF A FAMILY WITH MONILETHRIX

the body seems to be affected. A hair sample showed many moniliform hairs. Diagnosis: monilethrix.

II-5: Female, age 52 years. She appears to have normal dark hair, but as one of her sons has the disease fully developed there is no doubt that she carries the gene for monilethrix. On close examination a very small number (one per cent or less) of moniliform hairs are found. It is remarkable that a large number (about fifty per cent) of the non-moniliform hairs are thinner than normal, some showing slight thickenings at irregular intervals. Diagnosis: monilethrix, carrier.

III-1: Female, age 41, with fair hair. No moniliform hairs or keratosis.

III-2: Male, age 39, father of the propositus. At first sight he appears to have normal hair of dark color. On close inspection very slight keratosis is found, and microscopic examination of a hair sample reveals some (about five per cent) moniliform hairs. Diagnosis: monilethrix, carrier.

III-3: Female, age 24, with normal light brown hair and no keratosis.

III-4: Male, age 23, with normal fair hair and no keratosis.

III-5: Male, age 32, with normal fair hair and no keratosis.

III-6: Male, age 29, scalp sparsely covered by dark moniliform hair, especially marked over occiput where there is slight keratosis. Diagnosis: monilethrix.

III-7: Male, age 27, with normal fair hair and no keratosis.

IV-1: Male, age 18, with normal dark hair and no keratosis.

IV-2: Propositus, male, age 8 years. The scalp is sparsely covered by short dark moniliform hair. There is marked keratosis over the occiput and neck. The hair was normal at birth but became progressively abnormal after the sixth month. He is in good health and of normal intelligence. Diagnosis: monilethrix

IV-3: Female, age 5, with normal dark hair and no keratosis.

IV-4: Female, age 5, with normal fair hair and no keratosis.

COMMENT

The mode of inheritance is undoubtedly one of autosomal dominance, in agreement with the conclusion advanced by Cockayne (1933). The fact that monilethrix seems to skip a generation in some families was explained by Cockayne as probably due to incorrect information supplied by relatives. This is in fact what happened

in our family, II-5 and III-2 having been reported as normal by relatives. Irrefutable signs of activity of the gene for monilethrix could be demonstrated only after extremely close examination. In III-2 some keratosis was found over the occiput, but the hair was thought to be normal until microscopic examination revealed the existence of a few specific moniliform hairs. The number of moniliform hairs did not exceed five per cent in the sample studied, but it was obvious that many of the non-moniliform hairs were thinner than normal. Diagnosis was even more difficult in the case of II-5, as the small areas of keratosis were hidden by long dark hair. Thorough microscopic examination of a hair sample disclosed only a few typical beaded hairs, but many of the non-moniliform hairs were thinner than normal and constrictions at irregular intervals were observed in some.

From these observations we conclude: (1) that in the presence of the gene for monilethrix some keratosis may be present; (2) that the action of the gene on the hair is quite variable. Sometimes moniliform hairs are produced in a quantity great enough to result in typical monilethrix, while in other cases only a few typical moniliform hairs may be formed, but other hairs may be thinner than normal or constricted at irregular intervals. In the latter case the carrier of the monilethrix gene may be normal on superficial examination and reported as normal by relatives. It follows that a member of a monilethrix family may be classified as normal only after careful examination for keratosis and microscopic examination of a hair sample.

This brings us to the problem of the possible existence of a recessive form of monilethrix. A number of sibships are on record in which one or more children had monilethrix, but the parents and other relatives were reported to be normal. Cockayne (1933) tabulated 21 of these families and found that the parents were first cousins in two of the four families providing definite information on this point. Hanhart (1955) described typical monilethrix in two children of a sibship of four, whose parents were normal but were first cousins. These findings might suggest the existence of a rare recessive form in addition to the dominant form.

In the series of 21 sibships with normal parents tabulated by Cockayne, there were 31 affected and 42 normal offspring. The proportion of affected is .19 if minimum ascertainment is assumed and .35 if maximum ascertainment is assumed, hence the data may be considered to be in accord with the assumption of recessive inheritance.

Assuming that a recessive as well as a dominant form of monilethrix exists, it would be unlikely that both genes are located in the same chromosome. There is scanty evidence for an association between hair color and monilethrix. Anderson (1883) stated that in his family the 14 affected members were almost invariably dark haired, while the normal members had either fair or reddish hair. In our family all normal members with an affected parent have either fair or light brown hair (with the possible exception of II-1), while those with monilethrix were invariably dark haired. This association may be due to linkage, but the evidence is more indicative of pleiotropy. If it could be shown that in families with dominant monilethrix the gene for beaded hair is linked to the main gene for hair color, and that linkage is not present in cases of monilethrix confined to a single sibship, this would afford good evidence for the existence of a recessive type of monilethrix.

SUMMARY

A family with monilethrix due to a dominant gene is presented. The problems of carrier diagnosis, of the possible existence of a recessive form of the disease, and of the importance of establishing the possible linkage of dominant monilethrix with the main gene for hair color are discussed.

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An Investigation into the Genetics and Racial Variation of BAIB Excretion[1]

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INTRODUCTION

THE STUDY OF URINARY β-AMINOISOBUTYRIC acid (BAIB) excretion has progressed to the stage where there is no doubt that most of the variability between individuals in excretion rate of this substance is under genetic control. In fact, all studies to date have been in agreement with the monogenic hypothesis originally proposed by Harris (1953) (high excretors being homozygous for a single recessive gene and low excretors either homozygous or heterozygous for the dominant allele). However, since it was shown that the distribution of the variation in excretion rate of BAIB is continuous (Gartler 1956) and not dimorphic as assumed in earlier studies, it has become essential to ascertain whether this distribution is bimodal, which would be a requisite of a simple genetic hypothesis. Unfortunately most of the work to date on BAIB excretion has been carried out on Caucasoid populations, which are not suitable material for answering the question of bimodality since they contain such a low proportion of high excretors of BAIB. Work at this laboratory has shown that the Apache Indians of Arizona and the Black Caribs of British Honduras have relatively high excretion rates of this substance (Gartler, Firschein and Gidaspow 1956), and consequently it was felt that further work on these two populations would shed light on the problem posed above.

MATERIALS AND METHODS

Single urine specimens were collected from unrelated Apache Indians at the Fort Apache Reservation, Whiteriver, Arizona. Thymol was added to the specimens, after which they were stored in a deep freezer until ready for shipment (under dry ice) to the laboratory in New York. In British Honduras, single urine samples were collected mainly from complete family units (i.e., father, mother, and at least one child), plus a small number of unrelated individuals. Thymol was added to all samples and they were then stored in a refrigerator until shipment under ice to the laboratory in New York.

Creatinine determinations were run on all specimens utilizing the alkaline-picrate method. Aliquots of urine corresponding to various amounts of creatinine were then analyzed by two-dimensional chromatography with phenol and lutidine as solvents and with a 0.2 per cent solution of ninhydrin in acetone as a developer (Gartler 1956). The optical densities of BAIB and glycine were determined on all chromato-

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grams and the BAIB concentration expressed as the ratio of the optical density of BAIB/optical density of glycine. The use of an internal standard such as this permits greater accuracy than can ordinarily be achieved by paper chromatographic techniques. Also, since glycine is a constant and major constituent of the urinary amino acids, it was found that the BAIB concentration expressed in this manner corresponded closely to other methods of reporting its concentration (e.g., mg. BAIB/mg. creatinine).

All specimens were initially analyzed with aliquots of urine equivalent to .010 mg. of creatinine. On subsequent runs, the amount of urine applied was adjusted so as to give optical density readings within the range which we have found to yield a fairly linear response with changes in concentration. No lower limits were set on the amount of urine applied, but we have found that, for most urine specimens, satisfactory quantification cannot be obtained with an amount of urine equivalent to more than .020 mg. creatinine.

Overloading of the chromatogram can lead to serious quantitative errors, particularly in a genetic investigation. Urine specimens with high concentrations of the substance under investigation will be underestimated due to the very limited linear response range of optical readings on chromatograms. Samples with low concentrations will be overestimated due to interference from the numerous minor ninhydrin positive substances in urine which will appear when large amounts of urine are run. These errors will lead to a compression of the distribution and, if severe enough, can obscure the underlying genetic picture.

RESULTS

Bimodality of the distributions.

In figure 1 are given the distributions of the excretion rates of BAIB, reported as a ratio of the *optical density of BAIB/optical density of glycine*, for the Apache and Black Carib populations. As can be seen, both distributions are highly skewed with the long tail in the direction of higher values. In both cases, there is an indication of a dip in the distribution between .2 and .4 and a more detailed examination of this region revealed that these antimodal regions were real. This is better illustrated by plotting the logs of the excretion ratios, which essentially compresses the upper tails of the distributions. For simplicity in plotting, the excretion ratios were multiplied by 100 before taking their logs. In figure 2 such distributions are shown, and it can be seen that the distributions for both the Apache and Black Carib populations are definitely bimodal, though with considerable overlap in both distributions in the antimodal regions. The marked skewness of the original distributions essentially reflects the greater range of expression of high excretors of BAIB, which is what one might expect in the case of a physiologically conditioned genetic variable such as we are dealing with here.

Agreement of family data with bimodality of distribution.

The genetic validity of the bimodality in the preceding distributions depends on the absence of sex and age differences when individuals are classified according to

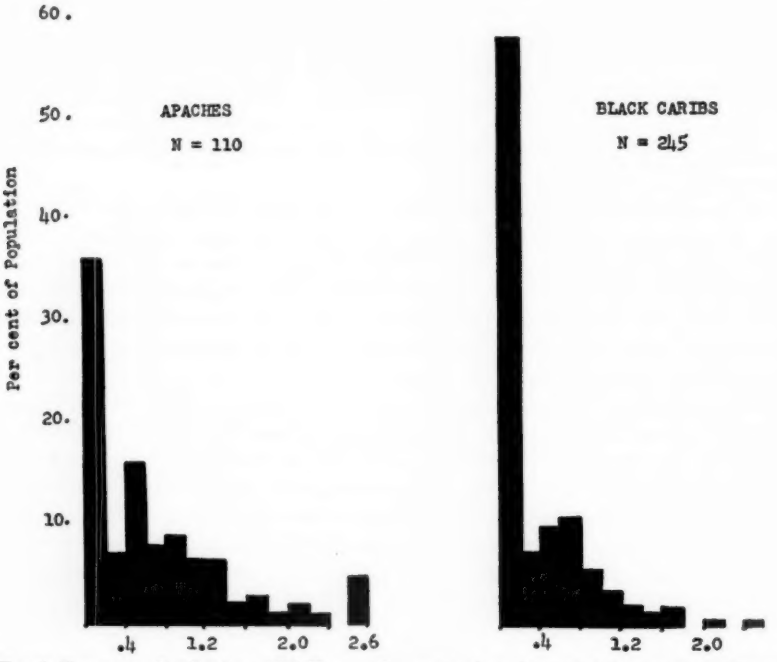

FIG. 1. Frequency distribution of BAIB excretion reported as the optical density BAIB/optical density glycine in the Apache and Black Carib populations.

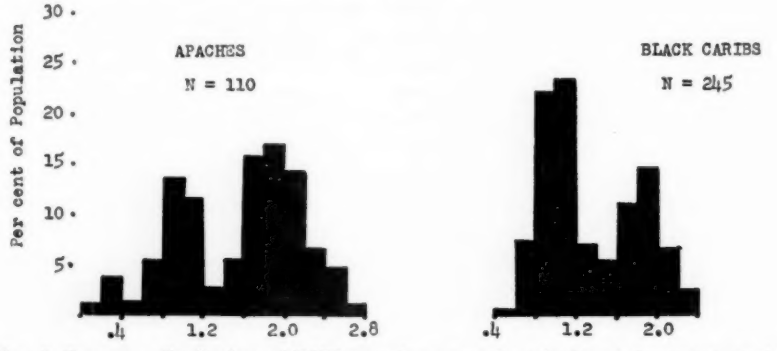

FIG. 2. Frequency distributions of BAIB excretion reported as the log of the optical density BAIB/optical density glycine in the Apache and Black Carib populations.

the observed antimode, and most important, on the agreement of family data with these distributions. These points will now be considered.

Except for the possibility of an increased proportion of high excretors among the very young (Calchi-Novati *et al* 1954; and Gartler, Firschein, and Gidaspow 1956),

no sex or age differences have been reported in any of the major studies on BAIB excretion. Due to the restricted age range in the Apache sample and the incomplete age data in the case of the Black Caribs, only very limited age testing was possible (5–34, and 35 or older for the Apaches; children and parents for the Black Caribs). These data are given in table 1, taking 1.40 on the logarithmic distribution as the dividing point between high and low excretors. As can be seen, there are no significant sex or age differences.

In table 2 the familial data for the Black Caribs are given. There are 5 families which would be classified as matings of high excretor by high excretor using the the dividing line of 1.40 (families 5, 10, 11, 26, and 35). According to genetic hypothesis, such matings should result in only high excretor offspring. Of the 26 offspring produced in these matings there are 24 high and 2 low excretors (families 10 and 35). The values for the 2 low excretors (.70 and .95) cannot be easily explained away by experimental error. However, in view of the known difficulties in collecting accurate family histories from such populations, it would seem premature at this time to consider these cases as real exceptions to the genetic hypothesis.

In table 3 the agreement of data from the remaining Carib families with a mono-factorial hypothesis is tested using 1.40 as the dividing line between high and low excretors. The agreement is good, as indicated by the non-significant chi-square of 2.37. In tables 4 and 5 the family data are further tested for agreement with the mono-factorial hypothesis by examining the distribution of high excretor offspring within segregating families according to the *a priori* method. As can be seen, the deviations from expected are clearly non-significant. The dividing point of 1.40 was initially selected, since it is the mid-point between the two modes. From the preceding results on age and sex testing, and the genetic analyses given in tables 3, 4, and 5, this dividing line of 1.40 appears to have genetic validity. Further support is given by dividing the distributions at 1.30 and 1.50 and carrying out similar analyses to those reported in table 3. The chi-squares obtained, though not significant, are higher (a chi-square of 3.16 for dividing at 1.30 and a chi-square of 4.72 for dividing

TABLE 1. PERCENTAGE OF HIGH EXCRETORS OF BAIB BY AGE AND SEX OF INDIVIDUALS

	Age Group	Sex	No.	High Excretors in per cent
Apaches	5–34	♀	50	50.0
		♂	33	63.7
	35 and over	♀	6	83.4
		♂	21	66.7
	Total	♀	56	53.6
		♂	54	64.8
Black Caribs	children	♀	96	39.6
		♂	83	42.2
	parents	♀	34	38.2
		♂	34	32.4
	Total	♀	130	39.3
		♂	117	39.3

$$\text{High Excretors} = \log \frac{\text{BAIB}}{\text{glycine}} > 1.40$$

TABLE 2. FAMILIAL DISTRIBUTION IN THE BLACK CARIBS OF BAIB EXCRETION $\left(\text{LOG } \frac{\text{OPTICAL DENSITY BAIB}}{\text{OPTICAL DENSITY GLYCINE}}\right)$

Family	Parents		Offspring									
	♂	♀										
1	2.22	1.15	1.96	.95	1.76							
2	1.26	.90	.70	1.04	1.86							
3	2.21	1.11	2.16	1.30	1.96	2.18						
4	.95	1.20	1.23	1.61								
5	1.75	1.41	1.45	1.91	1.87	1.94	2.06					
6	1.11	1.38	1.18	1.04	.70	1.18	.95					
7	1.08	1.08	1.26	1.73	1.65	1.72	1.00	.90	.90			
8	1.56	.95	1.00	1.00	.78	1.08						
9	1.28	.95	1.86	1.00	1.00	1.73	1.61					
10	1.48	1.98	.70	1.67	2.23	2.00	1.48					
11	1.81	2.04	1.83	2.10	2.08	1.86						
20	1.48	.95	1.50	1.91	1.78	1.78						
22	2.10	.90	1.97	1.04	.78	1.04	1.00	1.15				
23	1.15	1.84	1.96	1.26	1.89	1.04	1.70	1.08				
24	1.34	1.23	.78									
25	.70	1.00	1.21	.95	.78	.90						
26	1.84	1.43	1.63	1.88	1.90	1.67	1.83	1.83	1.81			
27	.95	1.00	1.08	.95	.95	.95	.84	.84	1.08	.84		
28	1.40	1.04	1.78	1.00	1.00	1.15	1.70	.95	1.20			
29	1.15	1.65	.90	.95	2.12	1.20						
31	1.04	1.49	1.20	1.04	1.26	1.20	1.08					
32	1.00	2.25	1.23	1.82	.78	1.90	1.08					
33	1.11	1.81	1.08	1.04	1.15	1.08						
34	1.15	1.00	.70	.95	1.00	1.59	1.28					
35	1.69	1.88	.95	1.93	2.06	1.62	1.41					
38	1.00	1.63	.90	1.48	1.65	1.38	1.00	1.38	1.78	1.15		
40	1.26	1.18	.78	.70	.70	.78	.90					
41	.90	1.69	2.03	1.94	2.02	1.21	.60					
45	.90	2.04	2.03	1.08	1.83	1.88	1.04	.95	.84	1.18	1.59	1.96
46	1.15	1.04	1.08	2.31	1.76	1.18						
47	1.00	.84	1.00	1.45	1.08	1.11	1.54					
48	2.10	1.18	1.18	1.11	1.23							

TABLE 3. TEST OF HYPOTHESIS THAT HIGH EXCRETION OF BAIB IS INHERITED AS A MENDELIAN RECESSIVE. TESTED ACCORDING TO FISHER (1939) ON THE BASIS OF A GENE FREQUENCY OF THE RECESSIVE ALLELE (t) OF .59

Mating	Class of Family	No. of Families		χ^2	Degrees of Freedom
		Observed	Expected		
T_ × T_	All children T_	5	7.722	2.362	1
	At least one child tt	8	5.278		
T_ × tt	All children T_	4	4.136	.006	1
	At least one child tt	11	10.594		

TABLE 4. ANALYSIS OF HIGH BY LOW EXCRETOR MATINGS WHERE AT LEAST ONE OFFSPRING IS A HIGH EXCRETOR

Family Size	No. of Families	No. of High Excretors Observed	No. of High Excretors Expected	Variance
3	1	2	1.72	0.49
4	3	8	6.40	2.35
5	2	5	5.16	2.16
6	2	4	6.09	2.76
8	1	3	4.02	1.94
10	1	5	5.00	2.49
Totals	10	27	28.39	12.19

TABLE 5. ANALYSIS OF LOW BY LOW EXCRETOR MATINGS WHERE AT LEAST ONE OFFSPRING IS A HIGH EXCRETOR

Family Size	No. of Families	No. of High Excretors Observed	No. of High Excretors Expected	Variance
2	1	1	1.14	0.12
3	1	1	1.30	0.26
4	1	2	1.46	0.42
5	3	6	4.92	1.78
7	2	5	4.04	1.94
Totals	8	15	12.86	4.52

at 1.50) and therefore indicate that the dividing point of 1.40 provides the better fit with the genetic hypothesis.

In this respect, it is of interest to estimate the frequency of misclassifications of high and low excretors using the dividing point of 1.40. By assuming normal distributions for the high and low excretors and calculating the proportion of the distributions extending on either side of the 1.40 line, the percentage of errors can be calculated. This procedure is well illustrated by Penrose (1951), and as applied to this data gives a frequency of misclassification of approximately 7 per cent.

DISCUSSION

The data presented strongly support the hypothesis that the major source of genetic variation underlying BAIB excretion is due to genetic differences at one locus. However, it is also clear from the continuous nature of the population distributions of BAIB excretion, and from the overlap between the modes in these distributions, that other sources of variation contribute to the observed differences between individuals.

Experimental errors and environmental variables are two definite sources of variation, although the exact magnitude of these factors are not known, Of major interest is the question of whether a more complicated genetic system, such as incomplete dominance, multiple alleles, or genetic modifiers might contribute to the continuity and overlapping of the bimodal distribution of BAIB excretion.

The possibility of incomplete dominance can be examined by comparing the mean value of low excretor parents who have had at least one high excretor offspring

(heterozygotes) with the mean value of low excretor parents who have had only low excretor offspring (mainly homozygous low excretors plus some heterozygotes). The mean excretion ratio of the known heterozygotes is 1.06 as compared with a value of 1.10 for that of the mixed group. The difference is not significant and in fact is in the opposite direction from that expected for incomplete dominance.

An examination of the potential contributions of multiple recessive alleles for high excretion and genetic modifiers to the variation in BAIB distribution can be made by carrying out an analysis of variance of only the high excretors from the three mating types producing them: (1) heterozygote X heterozygote, (2) heterozygote X homozygous recessive, and (3) homozygous recessive X homozygous recessive. If either multiple alleles or modifiers are important, then significant *between sibs: within sibs* variance ratios should be obtained in all three instances. If multiple alleles are the major modifying influence, then the three variance ratios should form a decreasing series from mating types 1 to 3, whereas with modifying genes, the variance ratios for the three mating types should not differ from each other. This last statement follows from a consideration of the number of high excretor types that can be produced by the different matings. In the case of multiple alleles each mating of type (1) could produce only one kind of high excretor, (2) could produce up to two kinds, and (3) could produce up to four kinds of high excretors. In the case of genetic modifiers, the number of high excretor types would depend on the number of modifying loci and would be independent of the three mating types. The variance ratios for the three matings are (1) 1.82, (2) 2.82, and (3) .96, only (2) being significant at the 5 percent level. These results would indicate that environmental variables and experimental errors are the major modifying forces involved in the observed bimodal distributions of BAIB excretion.

Although there is considerable overlap between the high and low excretor distributions of BAIB excretion, this genetic variable can still be of some importance in anthropo-genetic investigations. The racial variation indicated thus far (Sutton and Clark 1955; Gartler, Firschein, and Gidaspow 1956) covers a remarkably wide range, from less than 10 percent high excretors in Caucasoids to around 60 percent in Mongoloids, with Negroes somewhat intermediate. Furthermore, with improvement in techniques, it is likely that resolution of the high and low excretors can be much improved.

SUMMARY

Urinary BAIB excretion was studied in an Apache Indian (Arizona) and a Black Carib (British Honduras) population. Both populations exhibited bimodal distributions, though with considerable overlap between the two modes. The family data from the Black Carib population was shown to be in good agreement with a monogenic hypothesis, and the combined results were taken to indicate that the major source of genetic variation underlying BAIB excretion is due to genetic differences at one locus. Possible modifying forces causing overlap and continuity of the BAIB distribution, and the value of the BAIB excretion variable in anthropo-genetic investigations, were discussed.

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Genetic Implications of Certain Physiological Processes Affecting the Metabolism of L-Phenylalanine in Man[1]

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INTRODUCTION

THE MAINTENANCE OF THE PLASMA LEVEL of any metabolite, within certain limits, is largely under the control of three general processes: (1) the transfer of the metabolites into the blood, (2) the factors of intermediary metabolism affecting their plasma level, and (3) the renal excretion of these substances. A number of major, but rare, genetic variations are known which can affect these processes and subsequently influence the physiological homeostasis of the metabolite involved. However, since little is known of the role of hereditary differences underlying normal variation in these physiological processes, it was felt that an investigation of the nature of their normal variation would be worth while. Obviously these processes are in general quite complex, both physiologically and biochemically, but we are not so much concerned here with these complexities as with the relative pictures they present in terms of any underlying hereditary variability. Therefore, in this study we have either examined the overall processes, or else selected the major component involved.

Because the intermediary metabolism of L-phenylalanine is relatively well known, the specific problem taken for investigation was that of the physiological and biochemical processes regulating the plasma level of this amino acid. The actual mechanisms investigated were: (1) the rate of transfer of L-phenylalanine into the blood; (2) the conversion of L-phenylalanine to L-tyrosine; and (3) the renal excretion of L-phenylalanine.

METHODS AND ANALYSIS

Subjects. Monozygotic twins and like-sexed dizygotic twins were studied to evaluate the heritability of the above described stages. Monozygotic twins are particularly valuable in physiological experiments since they furnish an estimate of the repeatability of the experiment. The twins were all normal, caucasoid, young adults, of similar socio-economic backgrounds, residing in the New York City region. Each pair of co-twins was living together. Data on the zygosity, age, sex, and weight of these twins are listed in table 1. Their zygosity was established largely on the basis of blood typing, using the ABO, Rh, Kell, Duffy, Lewis, Kidd, MNS, and P systems.

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If a pair of twins disagreed in any of these blood groups, they were considered dizygotic. If a set of twins agreed in all blood groups tested, they were then subjected to further tests such as comparisons of fingerprint patterns, pigmentation, general morphological features, and phenylthiocarbamide tasting levels to confirm their monozygosity. To make certain that the subjects were in good health at the time of testing, they were given a general physical examination.

Samples of blood and urine. Each twin pair was tested at the same time, after overnight fasting of approximately 15 hours. To determine the fasting levels of phenylalanine and tyrosine in the blood and urine, 10 ml. of blood were drawn into heparinized tubes from a venipuncture and the bladder emptied. The subjects then drank 2 gms. of L-phenylalanine (Nutritional Biochemicals Corp.) dissolved in 200 ml. of water. After one hour, a second blood sample was taken and the bladder again emptied. The time interval of one hour was chosen on the basis of Jervis' (1947) work in which he showed that the plasma level of tyrosine was reasonably close to its peak one hour after the feeding of 5 gms. of DL-phenylalanine. The blood samples were immediately centrifuged and the plasma drawn off. Plasma and urine samples were frozen as soon as possible and stored in a freezer at $-10°C.$ until analysis.

Analysis of Plasma and Urine. The L-phenylalanine in the plasma and urine was assayed by a modification of the bacterial decarboxylation technique of Udenfriend and Cooper (1953). The addition of the acid alcohol was omitted as the final step, and the tubes were read in the spectrophotometer at 420 $m\mu$, directly after treatment with methyl orange. This modification was brought to our attention by Drs. Hsia and Troll who had used it with success in plasma phenylalanine determinations (Hsia *et al.*, 1956). The L-tyrosine in the plasma was analyzed by the nitroso-naphthol method of Udenfriend and Cooper (1952), and the L-tyrosine in the urine by a technique in which the tyrosine is separated from the urine as tyramine (Tashian, 1957) and subsequently assayed by the nitroso-naphthol method. The creatinine concentrations in the urine were determined colorimetrically by the alkaline-picrate technique. Urine values are always presented as creatinine ratios since this will have the effect of correcting for varying dilutions of the urine samples as well as any errors which may arise from incomplete emptying of the bladder.

Statistical Analysis. The data were subjected to an analysis of variance in which the mean inter-pair and mean intra-pair variances were calculated in all sets of twins for each of the factors measured. Inter-pair variances for both the monozygotic and dizygotic twins reflect environmental differences between pairs of twins and any genetic differences which may be present. The intra-pair variance for the monozygotic twins reflects only environmental differences, and only those acting within each set of twins. The intra-pair variance for the dizygotic twins consists of environmental differences within each set of twins and any genetic differences between the members of a set.

Since the inter-pair variances are compounded of both environmental and genetic components, they are of limited usefulness in arriving at any conclusions about hereditary contributions to variation. The best test in this respect consists of a comparison of the intra-pair variances of the dizygotic with those of the monozygotic twins. Here the environmental components cancel out, and any significant excess

TABLE 1. SUMMARY OF TWIN DATA AND FASTING (I) AND POST-FEEDING (II)* PLASMA AND URINE LEVELS OF L-PHENYLALANINE AND L-TYROSINE

Twin Pairs	Sex	Age (years)	Weight (lbs.)	Plasma (mg./100 ml.)				Urine (mg./mg. creatinine × 100)			
				Phenylalanine		Tyrosine		Phenylalanine		Tyrosine	
				I	II	I	II	I	II	I	II
MONOZYGOTIC TWINS											
1. A	♀	16	132	0.68	4.26	1.40	1.95	1.60	2.33	1.05	1.02
B			140	1.19	3.36	1.98	2.68	1.47	2.50	1.01	1.26
2. A	♂	16	154	1.59	3.65	1.50	2.15	2.00	3.81	2.88	2.98
B			150	1.63	4.14	1.85	2.28	2.56	5.67	3.33	3.59
3. A	♂	21	158	1.38	2.33	0.85	1.10	2.91	2.85	0.78	0.93
B			158	1.07	2.20	1.08	1.33	1.61	1.98	0.58	0.54
4. A	♂	20	157	1.38	2.83	1.43	1.85	1.43	2.34	0.89	0.99
B			151	1.32	2.83	1.38	1.75	1.29	1.38	0.99	0.95
5. A	♂	17	170	1.42	1.98	1.38	1.50	1.90	2.61	1.75	1.94
B			160	1.29	1.57	1.05	1.23	2.09	2.19	1.51	1.78
6. A	♀	16	115	1.48	3.68	1.05	1.70	1.93	2.69	1.24	1.50
B			116	1.46	6.64	0.90	1.73	1.37	2.53	0.93	1.03
7. A	♂	16	141	1.32	3.30	1.70	2.77	3.82	3.79	2.64	2.54
B			142	1.38	2.67	1.94	2.78	2.45	2.98	1.60	2.05
8. A	♂	17	160	1.42	2.89	1.47	1.85	1.20	1.99	1.03	0.83
B			147	1.36	3.18	1.18	1.95	1.51	2.36	0.74	0.98
9. A	♀	22	115	1.32	4.59	1.35	1.88	1.48	1.72	0.90	1.57
B			110	1.29	4.59	1.38	1.45	2.67	3.40	1.05	1.05
10. A	♀	22	133	1.42	3.68	1.48	1.85	1.49	4.88	2.93	3.72
B			120	1.19	3.71	1.05	1.88	1.84	3.99	1.54	2.85
DIZYGOTIC TWINS											
11. A	♀	23	110	1.38	4.72	1.18	2.00	1.28	2.74	0.69	0.91
B			110	1.42	6.19	1.20	1.78	1.84	2.65	1.08	1.04
12. A	♂	18	159	1.79	3.52	1.43	2.35	—	2.42	—	1.52
B			157	1.73	2.57	1.18	1.78	1.44	2.90	0.90	2.08
13. A	♂	15	122	1.23	3.93	1.63	2.80	6.02	8.67	1.43	4.69
B			121	1.13	3.40	1.35	2.23	3.16	5.00	0.79	1.67
14. A	♀	18	124	1.29	3.53	1.08					

13. A	♂	15	122	1.23	3.93	1.63	2.80	6.02	8.07	1.18	1.94
B			121	1.13	3.40	1.35	2.23	3.16	5.00	0.79	1.67
14. A	♀	18	124	1.29	3.52	1.08	2.38	1.78	2.45	0.66	1.07
B			121	1.26	3.49	0.88	1.58	1.98	3.54	0.81	1.40
15. A	♀	15	105	1.29	2.77	1.05	1.78	1.08	1.56	0.50	0.78
B			131	1.32	2.74	1.30	1.88	1.24	2.21	0.88	1.45
16. A	♀	18	120	1.13	5.31	1.43	1.93	1.49	3.65	0.85	1.04
B			131	0.85	3.24	1.13	1.83	2.28	4.17	0.93	1.04
17. A	♀	19	126	1.29	3.21	1.23	2.08	2.03	4.05	1.47	2.60
B			117	1.48	3.80	1.30	2.08	1.76	9.54	1.82	5.18
18. A	♂	16	219	1.35	2.10	1.33	1.88	1.56	2.20	2.39	2.16
B			173	1.50	2.98	1.28	1.70	1.19	1.76	0.97	1.49
Mean ± S.E. of mean				1.33±.04	3.49±.18	1.32±.05	1.94±.07	1.96±.16	3.26±.29	1.30±.12	1.78±.18

* One hour after the ingestion of 2 gms. of L-phenylalanine.

variance in the dizygotics can be attributed to genetic differences. Consequently, we have used the variance ratio (mean intra-pair variance for dizygotic twins: mean intra-pair variance for monozygotic twins) as an indication of genetic variability. A significant ratio as determined by the F test indicates that at least part of the observed variability is due to genetic differences.

A non-significant ratio does not mean that there is no genetic variation underlying the observed process. In fact, an excess of the intra-pair variance for dizygotic twins of that for monozygotic twins can be taken as an indication of genetic variation. Furthermore, because of the relatively small number of twin pairs investigated, a significant F ratio means that more than half of the observed variance is due to genetic differences. However, for the purpose of pointing out those characters desirable for more intensive genetic work, the criterion of a significant F ratio appears justifiable. We are also concerned in this study with the relative magnitude of genetic variability underlying the different processes investigated, and for this purpose a simple comparison of the different F ratios will suffice, that is, the higher the F ratio, the greater the contribution of genetic differences to the observed variation.

RESULTS

Table 1 lists the fasting and post-feeding plasma and urine levels for phenylalanine and tyrosine. The fasting values for plasma phenylalanine fell well within the ranges reported by Hsia *et al.* (1956) and Hsia and Driscoll (1956) who used an enzymatic decarboxylation technique similar to that employed in the present study. The fasting plasma tyrosine values were in agreement with those found by micro-biological assay (Harper *et al.*, 1952). Since values for urine are usually expressed in the literature as 24-hour samples we could not effectively compare the urine values found in these studies with those found by other workers.

The Transfer of Phenylalanine into the Blood

The actual increase over the fasting level, plus the converted phenylalanine present as tyrosine, was used as a measure of the diffusion of phenylalanine from the intestine into the blood. The transfer of this amino acid into the blood, one hour after its ingestion, ranged from .46 to 6.01 mg. per cent.

The mean intra-pair differences for the variation in the diffusion of phenylalanine from the intestine into the blood was .80 mg. per cent for the monozygotic twins and .93 mg. per cent for the dizygotic twins (table 2), the difference is not significant. Furthermore, the ratio of the intra-pair variances of the dizygotic twins to the monozygotic twins is .80, which is not significant and clearly not indicative of any significant genetic contribution to the observed variance. Consequently, it must be concluded that even though the variation observed in the rate of diffusion of phenylalanine into the blood was over a 13-fold range, this variation is largely due to environmental factors.

The Conversion of Phenylalanine to Tyrosine

The major factor of intermediary metabolism affecting the plasma level of phenylalanine is its hydroxylation to tyrosine, which is brought about by specific enzyme

systems present in the liver (Mitoma, 1956; Kaufman, 1957). Alternative pathways, if they exist (e.g., intestinal bacteria), must play a relatively minor role in this process, as indicated by studies on phenylketonurics (Udenfriend and Bessman, 1953) who have a genetic defect affecting this metabolic step. In these individuals, the conversion of ingested phenylalanine to tyrosine is less than 10 per cent of normals, which would be the upper limit for the contribution of alternative pathways of metabolism assuming the phenylalanine hydroxylase system in these cases to be completely defective.

In the present study, the conversion of phenylalanine to tyrosine was estimated by the increase in plasma tyrosine levels one hour after the ingestion of phenylalanine. The mean intra-pair differences for the variation in the increase of plasma tyrosine (table 2) was .22 mg. per cent for the monozygotic twins and .24 mg. per cent for the dizygotic twins, the difference is not significant. Furthermore, the ratio of the intra-pair variances of the dizygotic twins to the monozygotic twins is 1.16, which is not significant, and at best would indicate only relatively minor genetic contributions to the observed variance.

A possible objection to this analysis could be that there was considerable variation in the amount of phenylalanine available for conversion. However, when this factor was corrected for by dividing the increase in tyrosine by the increase in phenylalanine, the results were still not significantly different from the above findings. Another possible objection is that differential rates of metabolism of formed tyrosine (e.g., conversion to para-hydroxy phenylpyruvate) may exist which might give an erroneous picture of differences between individuals in their ability to convert phenylalanine to tyrosine, since variation in tyrosine degradation was not taken into account. It is doubtful, however, that possible differential rates of tyrosine metabolism would significantly alter our results because the metabolism of tyrosine is a second order effect in the metabolism of phenylalanine.

The Renal Excretion of Phenylalanine and Tyrosine

In the present study, the renal clearances were estimated in the following manner:

$$\frac{U/C}{P}$$

where U is the concentration of the amino acid in the urine, C is the creatinine concentration of the urine sample, and P is the amino acid concentration in the plasma

TABLE 2. MEAN INTRA-PAIR DIFFERENCES, MEAN INTER-PAIR (σ_p^2) AND MEAN INTRA-PAIR (σ_t^2) VARIANCES, AND INTRA-PAIR VARIANCE RATIOS FOR THE INCREASE OVER THE FASTING LEVEL OF L-PHENYLALANINE AND L-TYROSINE IN THE PLASMA ONE HOUR AFTER THE FEEDING OF L-PHENYLALANINE

	Dizygotic twins			Monozygotic Twins			Dizygotic σ_t^2 / Monozygotic σ_t^2
	Mean Differences	σ_t^2	σ_p^2	Mean Differences	σ_t^2	σ_p^2	
L-phenylalanine*	.93	.560	1.903	.80	.697	2.640	.80
L-tyrosine	.24	.043	.070	.22	.037	.119	1.16

* Actual rise in L-phenylalanine above the fasting level plus amount converted to L-tyrosine.

interpolated logarithmically at 5 minutes before the middle of the collection period (Smith, 1951). This is not a true renal clearance from a purely physiological standpoint; however, it is an expression of the rate at which the plasma is cleared, and for relative purposes, which are most important in this genetic study, it is adequate. Robson and Rose (1957) have successfully used urine creatinine concentrations for estimating the renal clearances of several amino acids.

Since tyrosine determinations were made on all blood and urine samples, it was possible to obtain clearance values for tyrosine as well as phenylalanine, and these will be discussed together. Because the renal clearances were estimated for the fasting state as well as after the levels of phenylalanine and tyrosine were increased, comparisons could be made of the processes affecting tubular reabsorption of these amino acids under both fasting and loading conditions.

The phenylalanine concentrations in both plasma and urine averaged higher than those for tyrosine, and, as expected, this was reflected in a greater mean renal clearance for phenylalanine than for tyrosine. It can be seen from table 3 that there was no marked change in the clearance values under plasma load since an almost complete reabsorption of these amino acids had taken place. This was so even though the loading stress was considerably disproportionate, the mean phenylalanine increase being about 3½ times as great as that for tyrosine. Similar results were reported by Doolan *et al.* (1955) who found no significant increase in the excretion of either tyrosine or phenylalanine when the plasma load of phenylalanine was three times that of tyrosine.

The mean intra-pair differences for the variation in the clearances of phenylalanine and tyrosine are given in table 4. Under fasting conditions, the mean intra-pair differences for the monozygotic twins were .43 mg. per cent (phenylalanine) and .22 mg. per cent (tyrosine); and for the dizygotic twins .70 mg. per cent (phenylalanine) and .37 mg. per cent (tyrosine). Though the dizygotic intra-pair differences are considerably greater than those of the monozygotics, the intra-pair variance ratios are not quite significant at the 5 per cent level (2.28 for phenylalanine and 2.89 for tyrosine). On the other hand, the means of the intra-pair differences for the post-feeding clearances were .33 mg. per cent (phenylalanine) and .20 mg. per cent (tyrosine) for the monozygotics, and .85 mg. per cent (phenylalanine) and .63 mg. per cent (tyrosine) for the dizygotics. The variance ratios for these differences are significant beyond the 0.5 per cent level (6.56 for phenylalanine and 10.13 for tyrosine).

TABLE 3. FASTING AND POST-FEEDING RENAL CLEARANCES AND PLASMA LOADS FOR L-PHENYLALANINE AND L-TYROSINE ONE HOUR AFTER THE FEEDING OF 2 GMS. OF L-PHENYLALANINE

	Fasting		Post-feeding		Plasma Load* (mg./100 ml.)	
	Range	Mean	Range	Mean	Range	Mean
L-phenylalanine	.79–4.89	1.58 ± .14	.76–4.36	1.69 ± .14	.28–5.18	2.15 ± .19
L-tyrosine	.48–2.17	1.05 ± .08	.46–3.28	1.17 ± .10	.07–1.17	.62 ± .05

* Increase over the fasting level.

TABLE 4. MEAN INTRA-PAIR DIFFERENCES, MEAN INTER-PAIR (σ_p^2) AND, MEAN INTRA-PAIR (σ_t^2) VARIANCES, AND INTRA-PAIR VARIANCE RATIOS FOR RENAL CLEARANCES OF L-PHENYLALANINE AND L-TYROSINE DURING FASTING (I) AND ONE HOUR AFTER FEEDING (II) OF 2 GMS. OF L-PHENYLALANINE

		Dizygotic Twins			Monozygotic Twins			Dizygotic σ_t^2 / Monozygotic σ_t^2
		Mean Differences	σ_t^2	σ_p^2	Mean Differences	σ_t^2	σ_p^2	
L-phenylalanine	I	.70	.480	2.128	.43	.211	.353	2.28
	II	.85	.584	2.100	.33	.089	.331	6.56*
L-tyrosine	I	.37	.107	0.170	.22	.037	.607	2.89
	II	.63	.324	0.749	.20	.032	.612	10.13*

* Significant beyond the 0.5% level.

It should be pointed out that the distribution of intra-pair differences among the dizygotic twins is quite irregular, with pairs 13, 16, and 17 accounting for most of the observed intra-pair variance in the post-feeding phenylalanine clearance, and pairs 13 and 17 being responsible in the case of the post-feeding tyrosine clearance. Heterogeneity of dizygotic twin intra-pair differences is of course expected in the case of genetic determination, the degree of heterogeneity being inversely related to the number of segregating factors, among other things. Although the heterogeneity is quite marked here, the present data are too limited to permit more than an indication of the above ramifications. Another and related point is the greater inter-pair variance of the dizygotic twins compared to the inter-pair variance of the monozygotic twins for the phenylalanine clearance (table 4). If anything, the monozygotic inter-pair variance should be the larger. Since individuals 13A and 17B of the above mentioned pairs, with their relatively high clearance values, are responsible for the greater inter-pair variance of the dizygotic twins, the problem of interpretation of the intra-pair differences in these pairs is raised. Clearly, the high clearance values of 13A and 17B are not peculiar to dizygotic twins. However, we are led to ask if these high clearance values are related to large intra-pair differences. That is, would such high individual values be accompanied by correspondingly large intra-pair differences if they were observed in monozygotic twins? Only further observations can answer this question. However, the fact that the data were collected under carefully controlled environmental conditions and that one dizygotic twin pair (16) exhibits a large intra-pair difference without any accompanying high clearance values, present evidence against this possibility. If pairs 13 and 17, which account for 25 per cent of the variation among the dizygotic twins, are not included in the calculations, the dizygotic/monozygotic intra-pair variance ratio for the post-feeding phenylalanine clearances, though no longer significant (1.89), still indicates considerable potential genetic contribution to the observed variance. In view of the preceding data and these latter considerations, it would appear that the overall picture indicates that the variation in clearance rates of phenylalanine and tyrosine are to some extent under genetic control, becoming markedly apparent when the filtration load is moderately increased.

It is of interest to notice the relationship between phenylalanine and tyrosine clearances under fasting and loading conditions. For this purpose, correlation co-

efficients were calculated between the phenylalanine and tyrosine clearances for the entire series of experimental subjects. The correlation coefficient between the clearances of phenylalanine and tyrosine during fasting was .83, and after feeding it was found to be .78; both correlations are significant at the 1 per cent level. These findings, in addition to the previously described genetic data on renal clearances, are not incompatible with the idea that some common mechanism is responsible for the reabsorption of these aromatic amino acids.

DISCUSSION

The observed variations between individuals in both the diffusion of phenylalanine into the blood and its subsequent conversion to tyrosine appear to be mainly attributable to differences which are largely environmental. It is solely in the excretion mechanisms of these amino acids that hereditary influences can be demonstrated. We should now like to consider briefly some of the possible explanations and implications of our findings.

One possible explanation of these results is that genetic differences appear only when the systems are under stresses not attained in the present work. For example, Hsia *et al.* (1956) were able to detect the presence of the mutant gene in people heterozygous for phenylketonuria by phenylalanine tolerance tests in which the average amounts of phenylalanine administered were about 3–4 times the amounts given in the present study.

Another possible explanation of these results is that genetic changes affecting renal excretion function are better tolerated by the organism than genetic changes affecting comparable stages in intermediary metabolism. For example, in renal glycosuria and cystinuria, both of which are hereditary defects involving renal function, the net reproductive capacity of affected individuals is not significantly impaired; while in glactosemia and phenylketonuria, which are hereditary defects involving steps in intermediary metabolism, the net reproductive capacity of affected individuals is markedly impaired. In this respect it is of interest to compare the effects of such genetic changes on the plasma level of the substance or substances involved. In cystinuria, where there is marked impairment of renal reabsorption of cystine, the plasma level of this substance is only slightly affected (Fowler et al., 1952) whereas in phenylketonuria, where the conversion of phenylalanine to tyrosine is almost completely blocked, the plasma phenylalanine level is increased over 20-fold. Another way then of stating this hypothesis is that the more important a physiological process is in maintaining the physiological homeostasis of the plasma level of an essential metabolite, the less tolerant it is to genetic change. Consequently, we might expect to find more genetic variation in the renal clearance of phenylalanine than in its oxidative metabolism to tyrosine.

SUMMARY

L-phenylalanine was orally administered to 10 sets of monozygotic and 8 sets of like-sexed dizygotic twins under fasting conditions. Pre- and post-feeding blood and urine samples were taken and analyzed for changes in phenylalanine and tyrosine levels. An analysis of variance for the observed variation in both the diffusion of

phenylalanine into the blood and its conversion to tyrosine gave no indication of genetic control of these processes. Under similar variance analysis, however, variations in the renal clearances of phenylalanine and tyrosine were found to be to some extent under genetic control. Evidence is presented to show that phenylalanine and tyrosine are possibly reabsorbed by a common tubular mechanism. The genetic and evolutionary implications of these findings are discussed.

ACKNOWLEDGMENTS

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Identical Twins Discordant for Interventricular Septal Defect and Absent Radius and Thumb

ROBERT M. STECHER[1, 2]

DURING THE LAST CENTURY it was customary to consider that deformities of new born children were hereditarily determined. This principle was first questioned by Jonathan Hutchinson who showed that children born with syphilis did not inherit the disease but received it as a transplacental infection in prenatal life. Within recent years many infections, rubella, toxoplasmosis, varicella, influenza, variola, vaccinia and herpes zoster, have been known to cross placental barriers to damage the fetus (Bass, 1952). Besides infections other forms of stress, injury, nutritional deficiencies and anoxemia during critical periods of pregnancy have been responsible, in experimental animals, at least, for congenital defects such as cataract, cleft palate, heart disease and other abnormalities (Ingalls, 1956). Some congenital defects appear to depend entirely upon prenatal environmental influence, others upon purely hereditary factors and still others upon a combination of such factors. In the case of hereditary diseases becoming manifest only in middle or later life the environmental factors are of increasing importance.

Twin studies are of great importance in determining the relative importance of heredity and environment. In identical twins concordance of genetic character is always greater than in fraternal twins. Discordance between identical twins is greater in conditions with an older age at onset than in conditions with a younger age at onset; indicating increased importance of environment. For these reasons it is important to describe and report all twins with discordance. The purpose of this study is to record a set of apparently identical twins, one normal, the other pathological in that he had a congenital interventricular septal defect and a deformed left arm and hand (Fig. 1). The latter is particularly interesting because three of nine siblings of these twins have congenital short thumbs (Fig. 2).

The twins under consideration were born to a gravida X para XI, thirty eight year old white mother in December 1955. All of the former children born of this marriage are living and well. The sex and year of birth of the children are as follows: 1. female, 1939; 2. female, 1941; 3. male, 1943; 4. male, 1944; 5. male, 1946; 6. female, 1947; 7. male, 1950; 8. female, 1952; 9. male, 1954; 10 and 11 male twins, 1955. They are interesting because of congenital short thumbs in three of them. The oldest child, a daughter has a short left thumb. The second child, another daughter, has bilateral short thumbs and the fourth child, a son, has a short right thumb. All of the remaining children have normal thumbs, although the eighth child, a daughter, was two years old and the ninth, a son, was less than a year old, making recognition of short

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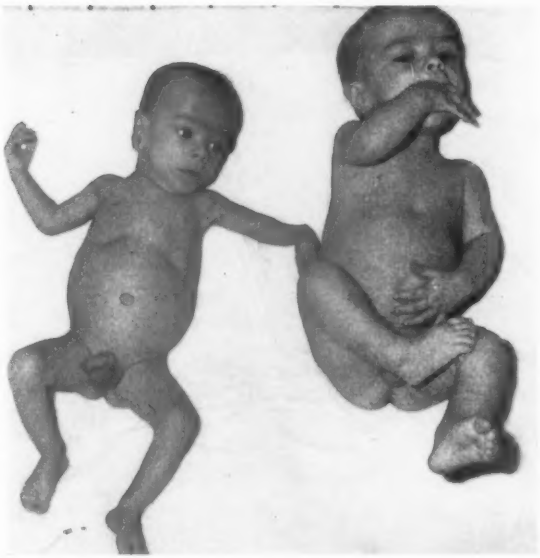

FIG. 1 PHOTOGRAPH OF BOTH TWINS AT 7 MONTHS, SHOWING MARKED DISPARITY IN SIZE, DEFECTIVE LEFT ARM AND HAND AND THE PROMINENCE OF THE FOREHEAD ON THE RIGHT SIDE OF THE AFFECTED TWIN, AND THE LEFT SIDE OF THE NORMAL TWIN.

thumbs difficult. Both parents and the maternal grandmother were examined and were found to have normal thumbs. No other history of anomalies of the fingers or toes was found in any ancestors or collateral relatives.

The last pregnancy was uneventful with no recallable prenatal infections or illnesses. The gestation period was 30 weeks. Hospital records are incomplete in that there is no comment about the character of the placenta but the mother was told shortly after delivery that her sons were identical twins.

Jan T., the normal and first born of the twins, was admitted for study July 25, 1956. His birth weight was reported to have been just under 6 pounds. He has been normal since birth. He was admitted to City Hospital for examination and comparison with his affected brother. Physical examination showed length 68 cm., sitting length 37.5 cm., weight 7005 gm, chest circumference 42 cm., head circumference 45.5 cm., temperature 36.7° C, pulse 140, respiration 40, blood pressure 90 mm Hg flush in legs. He was a well developed, well nourished, normal looking white male infant who could reach for objects, roll over alone and sit up with a little aid. He looked very much like his brother except for the difference in size, having the same color of hair and eyes, and the same facial and head contours, even to the asymmetrical rounded prominence of the left side of his forehead. The chest was clear. There was no cardiac enlargement. There was grade I blowing apical systolic murmur which was not transmitted. The rhythm was regular and the pulmonary second sound was louder than the aortic second sound. The remainder of the examination was

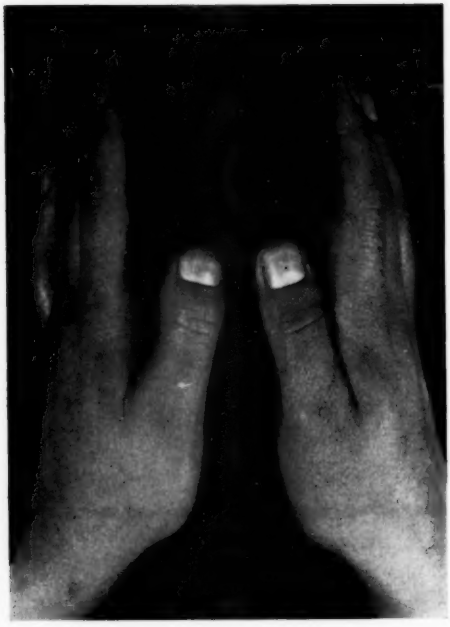

FIG. 2 THUMBS OF THE OLDEST SISTER OF THE TWINS SHOWING A CONGENITAL SHORT THUMB ON ONE HAND AND A NORMAL THUMB ON THE OTHER HAND.

normal. Laboratory studies revealed hemoglobin of 8.0 gm, white blood cell count of 12,000 per cu. mm. Urine was negative. Blood type was O, Rh negative (to D). Chest films and electrocardiograms were normal. Bone films showed no abnormalities and bone age was normal.

Jonathan T., the smaller twin was born two minutes after his normal brother. He weighted less than four pounds at birth. His progress was uneventful until the age of three months when he was brought to the Emergency Ward at City Hospital because of an upper respiratory infection. Examination at this time showed rales at the posterior left base and a low pitched grade II apical systolic murmur. A chest film showed pulmonary hyperemia consistent with a diagnosis of a bronchopneumonia and a left to right cardiac shunt. An electrocardiogram was definitely abnormal, showing "non-specific myocardial strain and possible left ventricular strain".

The left lower arm was deformed with a flail wrist joint. The hand was attached at right angles to the arm and abducted. There was a rudimentary left thumb consisting only of a small tab of skin which was removed at four months of age. Radiogram of the left arm showed absence of the left radius and absence of all bones of the thumb (Fig. 3).

After the pneumonia cleared up the patient was followed in the clinic and was given a cast for the deformed left arm and hand. At ages four and five months he was readmitted because of bronchopneumonia and congestive failure. He responded

FIG. 3 RADIOGRAMS OF THE ARMS OF THE AFFECTED TWIN SHOWING ABSENCE OF THE RADIUS AND OF ALL THE BONES OF THE THUMB.

well to therapy each time. Radiograms showed cardiac hypertrophy or dilatation with predominantly left ventricular enlargement. Cardiac catheterization was consistent with an interventricular septal defect.

The patient was admitted to Cleveland City Hospital July 25, 1956, at the age of seven months, for cardiac surgery. Physical examination at this time showed length 57 cm., sitting length 37 cm., weight 4300 gm., chest circumference 35.0 cm., head circumference 39.5 cm., temperature 36.7°C, pulse 140, respiration 40, blood pressure 90 mm. Hg flush in arms, 70 mm. Hg flush in legs. He was a poorly developed, poorly nourished marasmic seven month old white infant who followed objects with his eyes and occasionally reached for objects held in his way. His eyes were brown and his hair was brown. He showed a rounded asymmetrical priminence of the right side of his forehead. There were moist rales in the left anterior chest and all over the posterior chest. The heart was enlarged to the anterior axillary line in the sixth intercostal space. No thrill was felt. A grade III low-pitched blowing systolic murmur was heard along the left sternal border and the pulmonary second sound was louder than the aortic second sound. The liver extended two fingerbreadths below the costal margin. The left arm and wrist were as has been described. Laboratory studies revealed hemoglobin of 6.5 gm., white blood cell count of 12,150 per cu. mm., urine normal. Blood type was type O, Rh negative (to D). Chest films showed cardiac

hypertrophy and dilatation, left pleural effusion, passive hyperemia and possible bronchopneumonia. Bone films showed a missing left radius, missing left thumb and a bone age of 3 months. Electrocardiogram showed right ventricular hypertrophy. He was treated with antibiotics, humidity, digitalis and several blood transfusions. On July 26, 1956 he was taken to the operating room for repair of the interventricular septal defect. He died shortly after the operation was finished. Autopsy showed an interventricular septal defect which had been repaired.

The diagnosis of zygosity is usually relative. It can be made with complete certainty only by cross transplantation of skin grafts or of a kidney which grow only in monozygotic twins. The clinical diagnosis depends heavily upon the general physical characteristics of the twins, eye color and iris pattern, hair color, skin color, and facial and bodily appearance. Evidence becomes more convincing for monozygosity when there is complete concordance for all of the blood groups. The twins under discussion were of blood group O and Rh negative, these being the only groups tested. Hair and eye color were identical. There was the asymmetry of the head, a prominence of one side of the forehead mirror imaged in the two individuals. There was also the impression of monozygosity expressed by the delivering physician. Though it is by no means scientifically proven it seems safe to assume that this was a set of monozygotic twins.

The fact that one heart was normal indicates that the interventricular septal defect in the affected twin was largely if not entirely due to environmental factors during pregnancy about the eighth week of gestation. The defective left arm and hand in the same individual can be ascribed to the same cause.

Since three of his ten siblings have a short thumb the question arises as to whether or not the deformity of his left arm, an absent radius and an absent or rudimentary thumb can be an unusually severe expression of the short thumb syndrome. A study of over 100 patients with short thumbs shows that they vary in expression only as to whether they involve the right thumb, both thumbs or the left thumb. The deformity of the short thumb depends entirely upon the shortness of the terminal phalanx, this being remarkably constant at about two thirds of the length of a normal phalanx. There are no other discernible defects. Preliminary investigation shows that this is inherited as a single factor autosomal recessive trait. No ready explanation suggests itself as to why it manifests itself in about half the cases as a unilateral defect. Associated characteristics so far observed include shortness of terminal phalanges of the middle fingers, short fourth or fifth metacarpal bones, short terminal phalanges of the great toe, or short metatarsal bones of the great toe, the fourth toe or the fifth toe. Since no other variation in the expression of short thumbs has been observed in a considerable series and since no case of congenital absence of the thumb or radius is recorded in this series, it is assumed that the short thumbs found in this family are not related to the absence of the thumb and radius observed in the affected twin.

In a short review of the literature, Dodson (1956) states that absence of the radius is a well known but fairly rare defect. In 1924 Kato reported a total of 253 cases. Birch-Jensen (1949) reported 73 cases in Denmark and thought the prevalence in the Danish population was 1 in 55,000. Because of the high death rate early in life

he estimated the incidence at birth as 1 in 30,000. Birch-Jensen found that most of the pedigrees showed dominant inheritance but a few suggested recessive inheritance. One half of his cases were sporadic and he thought these were non-genetic. The sporadic cases and the presumed recessive ones could be explained on the basis of a dominant mutation in one of the parents.

Dodson described a father with bilateral absence of radii and thumbs who had four affected out of six children, the last case being one of discordant fraternal twins. The first child with unilateral deformity died of bronchopneumonia at three months of age. The second child, a girl, is still living and the deformity has been fairly successfully corrected. The fourth child has only one absent thumb. The propositus died at 6 months of age. Birch-Jensen found a high mortality in cases of congenital absence of the radius as evidenced by the age of distribution of the propositi, over 60 per cent of them being twenty or younger. He explained this on the basis of increased incidence of other defects, especially congenital heart disease.

It is assumed that this monozygotic twin suffered a nutritional, circulatory, infectious or traumatic incident about the eighth week of gestation resulting in defective development of the left hand and arm and the other twin escaped this effect. This could have been a disadvantageous position in the uterus, a temporary partial kinking of the umbilical cord or a significant placental infarct.

SUMMARY

A set of identical twins is described, one normal, the other with a congenital absence of the left radius and thumb and a congenital interventricular septal cardiac defect. This twin was definitely smaller than his brother, he suffered repeated upper respiratory infections and he died immediately after a surgical operation to correct his cardiac defect.

The evidence for monozygosity includes similarity of hair and eye color, facial and head contours and identity for ABO blood group and reaction to Anti-D. Other blood groups were not investigated.

Three other siblings in this family have congenital short thumbs thought to be unrelated to the absent radius and thumb. The affected twin had congenital cardiac defect and died young, characteristic associations which have been noted by others is association with congenital absence of the radius.

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BOOK REVIEWS

The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki

By J. V. NEEL AND W. J. SCHULL. Publication No. 461, National Academy of Sciences-National Research Council, Washington D. C., 1956. 241 pp. $2.00.

ANY reader of this report will be immediately impressed by the tremendous difficulties that were encountered—and surmounted—in the study. He will also be impressed by the size of the program. He will further be impressed by the care and attention to detail in the planning of the study. Finally he will surely be impressed with the cooperation of the Japanese —physicians, midwives, and mothers—during the stress of the post war reconstruction.

When the study began the likelihood of demonstrating any genetic effects of radiation seemed extremely small. Nevertheless the program was started, on the recommendation of an *ad hoc* genetics conference, which stated: "Although there is every reason to infer that genetic effects can be produced and have been produced in man by atomic radiation, nevertheless the conference wishes to make it clear that it cannot guarantee significant results from this or any other study on the Japanese material. In contrast to laboratory data, this material is too much influenced by extraneous variables and too little adapted to disclosing genetic effects. In spite of these facts, the conference feels that this unique possibility for demonstrating genetic effects caused by atomic radiation should not be lost." The study actually got under way in 1948 and continued until February 1954.

Despite the fact that 75,000 pregnancies were registered, the opportunity for demonstrating genetic effects was not great, for most were from areas with little radiation. The number from heavily radiated areas who survived and had children was quite small, so that only large effects would be statistically significant.

This book gives in great detail (241 pp.) the findings of the study. Following two chapters on the background and general plan of the project, there is a chapter on the history and ethnology of the two cities, two chapters on radiation measurements, one on statistical methods, and then separate chapters on each of the criteria of genetic damage—sex ratio, malformations, stillbirths, infant deaths, and anthropometrics. The last three chapters are a summary of autopsy findings, a recapitulation, and a final verdict entitled "Permissible Inferences".

A study of this magnitude and with as many unavoidable uncertainties must depend on a number of arbitrary choices. The assignment of radiation amounts was done by placing each person in one of five broad categories, based on distance, shielding and symptoms. Group 1 consisted of those outside the cities. Groups 2, 3, and 4 consisted, successively, of those closer to the hypocenter and with less shielding. Class 5, curiously, includes all who had any symptoms (epilation, petechiae, or gingivitis) irrespective of distance, except that those more than 3000 meters away were assumed to have had symptoms for reasons other than radiation. The five classes are estimated to have received respectively, a negligible amount, 5–10 reps, 50–100 reps, 100–150 reps, and 200–300 reps. The principal radiation difference in the two cities was that the Uranium-235 bomb in Hiroshima produced relatively more neutrons than the Plutonium-239 bomb at Nagasaki.

The analytical and statistical procedures are all on the side of extreme conservatism, in the sense that great precaution is taken against wrongly concluding that there were sig-

nificant radiation effects. The various groups were all checked for comparability in many other variables (e.g., maternal and paternal age, parity, economic status, induced abortions, maternal syphilis, and parental consanguinity). Where important these factors were taken account of by adding additional levels of classification, by covariance analysis, or (as with the consanguinity data) by simply excluding these individuals. Independence of various tests was insured by sorting the data in such a way as to have non-overlapping indicators. For example, a stillborn child with a malformation was counted only once, as a malformation but not as a stillbirth. All these precautions resulted in loss of some data.

The general conclusions of the study are now well known to geneticists: none of the indicators showed a clear statistical significance. The only possible exception to this was the sex-ratio change following exposure of the mother. There was the expected reduction in male children in the heavily exposed groups, but the statistical significance is borderline and differs for different ways of analysis, several of which are given. Furthermore, a subsequent study for two more years failed to confirm the difference.

The principal comment that I have on the analysis and report is this: since it was almost a foregone conclusion that none of the indicators would show a significant difference, and since everybody hopes the "experiment" will never be repeated, the analysis might have been done in such a way as to get the best estimates the data can afford. I believe more information might have been extracted if each person had been assigned an estimated dosage, however much this might have been in error, rather than having been grouped into such broad and arbitrary classes. The assignment could have used distance, shielding, and severity of symptoms in a quantitative way. It would then have been possible to estimate, by regression methods, the amount of effect per roentgen with appropriate confidence limits. In my opinion a change of emphasis from one of testing the null hypothesis to one of estimating as well as possible the range of possible effects would have provided more useful information from the data. However, the burden of responsibility lies somewhat on him who would suggest an alternative procedure, for the authors state that any investigator who wishes to try other analytical methods may obtain a duplicate set of the IBM cards on which the original analysis was based.

From the data provided in the book one can make the following statements with roughly 95 per cent "confidence". The amount of radiation received (estimated to average about 100 r) did not cause more than a 1.6 per cent change in sex ratio following maternal exposure to radiation, or four per cent following paternal exposure; the malformation rate was not more than doubled; the stillbirth and neonatal death rates were not increased by more than 80 per cent. Predictions from mouse data would fall within these ranges.

In the final chapter, entitled "Permissible Inferences", the authors state their opinions as to what conclusions about radiation effects in man may be drawn from this (and other) studies. There are a number of minor points that I would disagree with, and the section on natural selection in man seems to me to be largely an extensive elaboration of the obvious and unnecessarily critical of some of Muller's writing. However, the main purpose of this chapter is to point out the uncertainty of quantitative information on total radiation damage, even in experimental animals. Although some of the instances quoted by the authors as examples of the wide range of permissible inferences seem to me to be extreme, no one can disagree with their conclusion that present information is far from adequate.

In view of this inadequacy, the authors question the wisdom of any quantitative inferences about radiation effects in men, saying "there is doubt about the advisability of calculations which have the appearance of mathematical exactitude to persons not thoroughly indoctrinated in genetics and unfamiliar with the shaky basis of the primary assumptions . . . there is, on the other hand, the possibility that by refusing to be drawn into

premature speculative calculations which in the nature of things will be 'used' as soon as they have been set to paper, and by insisting on all possible occasions that the work that should be done actually be carried forward, the geneticist in the long run will arrive more quickly at the goal of a lasting, valid appraisal of this problem." My own opinion is that our information is likely to be inadequate for some time, that quantitative estimates may serve as guides and stimuli to further research, and that when there are decisions to be made provisional and inaccurate quantitative estimates are better than none at all.

As a final point, I should like to call attention to another consequence of the foresight of those who planned these studies. There are many data, by-products of the main study, that are of great genetic interest. For example, the figures provide abundant information on the effects of maternal and paternal age, and of parity on each of the indicators. Perhaps most useful of all are the consanguinity data. The high rate of consanguineous marriage together with complete registration and medical examination make possible a large and useful body of data.

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Genetic Mechanisms: Structure and Function

Cold Spring Harbor Symposia on Quantitative Biology. Vol. 21. Cold Spring Harbor, New York: The Biological Laboratory, 1956. pp. xviii + 392, 194 figures and 2 plates, $8.00.

MOST workers in human genetics probably feel an occasional pang of nostalgia for their college or graduate school days of experimental genetics: for the satisfying ratios from an ear of corn or a bottle of flies, the simple cytological techniques of *Tradescantia*, or perhaps the overnight experiments with *E. coli*. Most have maintained only a limited contact with recent progress in the genetics of laboratory organisms. On attending or reading this sort of symposium we are likely to be thrilled both by the astonishing advances and by the beautifully designed experiments. The ingenuity of the microbial geneticists rivals that of Pasteur, and experiments on higher organisms give a steady yield of vital new concepts.

The human geneticist can perhaps congratulate himself on one point: complex scientific problems usually have simple solutions. With respect to genes and chromosomes, most of the problems must be solved by the experimentalists, and only the solutions are likely to concern the human geneticist. This review will sample the problems and emerging concepts presented in the 29 papers by some 40 authors.

Protein-free deoxyribonucleic acid (DNA) can transmit genetic information, but it can function as a gene only in intimate association with protein and protein synthesis. This protein synthesis is under intensive study. When genes are active, they often accumulate protein around them as exemplified by nucleoli and by "puffing" of certain loci in the giant chromosomes. When protein synthesis is stopped in isolated mammalian nuclei by digestion of DNA, synthesis can be restored by addition of heterologous DNA fragments or even by RNA. But ultraviolet light seems to kill bacteria by temporarily halting all DNA synthesis, while other syntheses proceed and unbalance the system. Proteins and nucleic acids can also be synthesized in enucleated cells.

The confusing varieties of recombination in bacteria are now all seen to involve the

fragmentary transfer of genetic material. They are aptly characterized by the term *meromixis*.

The Watson-Crick model of DNA is meeting new problems in its application to chromosomes, although the original difficulty of explaining separation of the helices has been overcome. DNA seems to occur in discrete molecules along the chromosome, and evidence for crossing over within such units may eventually be explained as "gene conversion"; at least, nonreciprocal recombination is established in yeast. Evidence from bacteriophage shows that reverse mutation, restoring a mutated gene to its normal state, may sometimes be more probable than the original mutation.

As for nomenclature, the Rh problem is duplicated in the histocompatibility factors of mice. The mouse geneticists have used Fisher-Race style capital letters for antigens and phenotypes, and symbols like Wiener's for the controlling alleles. Now crossing over has been found, and revision of the symbols is imminent. Seemingly only L. C. Dunn had courage to define the gene. Definitions based on the unit of function, the unit of mutation, or the unit of recombination have proved mutually inconsistent. In the transition period, while it is still conceivable that some genes may be simple units, Dunn would designate as *complex genes* those "elements within which the changes are related as variations on a common theme, and in which the parts can be identified individually by recombination or complementarity."

Experimental embryology continues to multiply the complexity of interactions during development, and many mutations are yielding to analysis on this level. Differentiations induced by these processes are sometimes quite irreversible, and evidence from several sources, especially corn, is revealing complex nuclear mechanisms which may be involved in these changes of nuclear potentials.

Dramatic proof of irreversible differentiation was reported by King and Briggs. They transferred nuclei from frog blastulae to enucleated eggs and obtained a high proportion of normal tadpoles. Similar implantation of nuclei from endoderm of late gastrulae did not usually support normal development beyond the blastula stage. Nuclei from such "endoderm blastulae" were again implanted in enucleated eggs, and the cycle repeated up to five times. The descendants behaved like the original endoderm nuclei, and often yielded clones of embryos with a constant developmental defect.

As usual in this series, the editors have struck a satisfying compromise between recording the symposium verbatim and excluding all discussion. A good ten-page author and subject index makes the volume a ready reference to the latest concepts and discoveries in microbial, biochemical and developmental genetics.

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Fertilization

By LORD ROTHSCHILD. New York: John Wiley and Sons, Inc. 1956, pp. 170, $3.50

LORD ROTHSCHILD states, in the preface, that this book is intended for those interested in general biological problems, particularly those of general and cellular physiology and biochemistry. The book is limited to the "life of the egg from the attachment of the fertilizing spermatozoon or the apposition of the male and female pronuclei." The discussion is still further limited by the exclusion of crustacea and sponges, and of asters and origin of first cleavage amphiasters, gynogenesis and androgenesis, merogony, parthenogenesis (not entirely), and plant fertilization (again, not entirely). The reference materials are limited to

those works which are more recent, more complete and those considered most experimentally valid. The author does, however, cite some work which he criticizes from the standpoint of either the experiments performed or the conclusions drawn, therefore, the book is not a simple listing of work done in the field in the past twenty-five years. This attitude is stimulating to the reader, making him evaluate the experiments cited and the author's conclusions. This pruning of the literature makes the book more readable there being fewer experiments and authors to becloud issues.

The first chapter is on the grosser aspects of fertilization and discusses morphology, membranes and fertilization cones. Rothschild's statement that the movement of the male pronucleus is mechanical "caused by the growth of the sperm aster (only, of course, in those cases where a sperm aster exists)" appears contradictory and open to question. Sperm-egg interacting substances are discussed in the next three chapters. This discussion included two chapters on plants. These chapters are followed by three chapters on gross egg metabolism and the more specific metabolism of amino acids, carbohydrates, and fats both before and immediately after fertilization. Chapter 8 is a special consideration of the chemistry and structure of the egg cortex and Chapter 9 is an extension of this in its discussion of blocks to polyspermy. The next chapter is concerned with bioelectric potentials. The author does not believe that fertilization is either the result of such potentials or that it might cause membrane changes which could produce potential differences and action currents. He cites as reasons for this opinion the difficulty of measurements on small eggs and the poor to negative results to date. He argues that different ionic concentrations inside and outside the cell need not necessarily mean that the membrane must show a potential difference across it. At the end of the chapter, Rothschild cites recent measurements on sea urchin eggs demonstrating substantial potential differences across the egg membrane. These he considers important but says they do not affect his conclusions. Confirmation of these observations may cause Lord Rothschild to change his viewpoint, because such potential differences have been found extensively in both the plant and animal kingdoms. Chapter 11, on the specificity of fertilization, should possibly have followed directly the one on polyspermy since the problems are so similar. The final chapter is a brief statement of fields for future investigations which might contribute enough data to allow for the formulation of a good theory of fertilization. The author makes a plea for studies which use "any eggs other than those of echinoderms," a plea which would be heartily seconded by an ecologist working near a marine biological station.

There is an extensive list of references including a record of their citations in the text. This is followed by a list of plants and animals including latin names, common names, class and order as well as the pages in the text where the organism is mentioned. There is also a general index.

Through the book, Rothschild emphasizes the necessity of standard treatment of the material before its use. Varieties of treatment (i.e. starvation of animals before eggs or sperm are taken) produce much variability in the reported results. This, combined with different sources (and presumably different genetic populations, though this is not mentioned) of the same species and the use of different species, make it difficult to obtain clearly comparable data.

The reviewer strongly recommends the book because of its stimulating view of a field which is beginning a new phase of physical and chemical experimentation to which the author is an outstanding contributor.

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RH-HR: Sus Tipos y Applicaciones

By A.S. WIENER. Translation by Darwin Molins, revised by Frederico Marín. México: La Prensa Médica Méxicana, 1956, Pp. 120 + xvi, 3.50 U. S. Cy.

THIS is the Spanish version of a book that has been translated into German and is scheduled to appear also in Japanese. The original English version was reviewed in these pages (Am. J. Human Genetics 1954, 6: 363–4), and the characterization of it there ("essentially a series of definitions of terms of common occurrence in Dr. Wiener's writing about the Rh-Hr blood groups") is still applicable. But my statement that the "reader will not find this book of much help in understanding the publications of the British workers" is more than ever an understatement, for the reader will surely find the Spanish version a positive hindrance. To the material originally devoted to anti-CDE polemics (about 5.6 per cent of the text) there has been added 20 new pages devoted to this subject, raising the percentage of polemical material (in a "syllabus") to some 23 per cent. This doubtless reflects Dr. Wiener's growing preoccupation with the controversy over notation. It is hard to predict what will be the effect of all this on foreign-language audiences, but one wonders if Dr. Wiener has considered the possibility of a "the lady doth protest too much" reaction.

WILLIAM C. BOYD
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Human Blood Groups and Inheritance.

By SYLVIA D. LAWLER AND L. J. LAWLER. Cambridge: Harvard University Press. 1957. $1.50.

THIS book is another example of the gift for popular exposition in which the British seem consistently to excell the Americans. In the space of 95 pages, Dr. Lawler and her husband manage to discuss the history of blood grouping, the techniques, the ABO system, the MNS blood group system, the Rh blood group system, other blood group systems, the (British) National Blood Transfusion Service, and blood groups and biology. The treatment is so simple that any reader with a college education should be able to follow it, yet an astonishing amount of information is presented. There are good illustrations, a glossary, and an index. The new ideas on the chromosome number in man are referred to.

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Population Genetics: The Nature and Causes of Genetic Variability in Populations.

Cold Spring Harbor Symposia on Quantitative Biology. Vol. XX, 1955. Cold Spring Harbor, L.I., New York: The Biological Laboratory. $8.00.

THIS volume provides a panoramic view of the fields of population and quantitative genetics. The organization of the symposium into sections of four or five papers with a synthesis of each section and two general surveys (by Dobzhansky and Lerner) makes the proceedings a coherent whole, despite the breadth of the field, and presents a balanced view of the progress, controversial issues, and active spheres of investigation.

The most exciting idea which runs through this symposium is the concept of the Mendelian population as a biological entity on a different level from the individual organism—a highly integrated system adjusting to an environment which is variable in space and time, with its own laws of development and change not directly deducible from the individual biology of its members.

Dobzhansky points out, that contrary to the classical view of a population as consisting of a wild type plus some mutants which have not yet been fixed or eliminated, the apparent homogeneity of wild populations hides a great deal of genetic variability, chromosomal polymorphism, and heterozygosis.

Dempster discusses the ways in which heterogeneity is maintained, including the balance of selection and mutation, heterosis, multiplicity of ecological niches, variable selection pressure, selection depending on gene frequencies, and antagonistic gametic and zygotic selection. Prevesti and Buzzanti-Traverse examine aspects of genetic heterogeneity in space and time. Allison considers the factors which maintain polymorphism at the sickle cell and thalassemia loci in man in Africa, where he considers it to be an equillibrium condition due to heterosis, and in the United States Negro population, where he regards it as a transient phenomenon.

If the situation described by Allison is as widespread in man as it seems to be in other organisms, then the persistence of genes which are deleterious, even lethal, in the homozygous condition cannot be attributed to recent mutation and the frequencies of such genes cannot be used to estimate the rate of mutation in man. Furthermore, any program of eugenics must consider the total effect of a gene in its population, not only in the homozygote.

Of special interest for the human geneticist is the approach to a quantitative theory of competition within populations (Sakai) and between populations (Wright). Since intrapopulation selection is weaker in small populations, and since interaction terms in the fitness of human populations are especially important, this line of inquiry will facilitate the quantitative study of human evolution.

The mathematical models have come a long way since the Hardy-Weinberg law. The equations have become more complex as terms representing degrees of dominance, linkage, epistasis, systems of mating and different types of systematic pressure have been introduced. The growing complexity makes even more important the close collaboration of the mathematical and experimental geneticists if the theoretical advances are to find application. Many of the participants noted and deplored the fact that we have no estimates for many of the theoretical parameters, and that most breeding work is not based on the mathematical theory. The papers by Wright, Kimura, and Hayman contribute to the streamlining of the mathematics.

The selection experiments by Manning in cotton, Robinson and Comstock and Bell, Moore and Warren in corn, Robertson in Drosophila, Falconer in mice and Dickerson in poultry differ in methods and results but agree in emphasizing the significance of population structure (especially the organization of variability) in determining the response to selection. Mather notes the need for a theory which would permit the prediction of the parameters of population structure from the past history of the organism.

Sheppard discusses the evolution of closer linkage in human blood groups as a stage in the formation of super genes.

Carson reports on the marginal populations of Drosophila, which he shows to be more homogenous cytologically, with fewer restrictions to recombination and therefore potentially more variable than the more specialized central populations. Thus a population has a spacial structure of historic origin which may provide a clue to a general view of the ontogeny of populations.

The final section deals with the integration of genotypes. Wallace and Vetukhiv describe three levels of integration based on epistasis of homozygous loci, coadaptation of gene blocks within a population, and integration of whole gene pools through selection for heterozygosity. Thoday shows that developmental homeostasis (as measured by bilateral asymmetry of bristle number) declined in the course of selection of several lines of flies for high or low bristle number, and that this decline is not eliminated by crossing. King's experiments with DDT resistance show that moderate selection can be more effective than intense selection.

The closer integration of human with general population genetics can be expected to result in heterosis for both fields. The human geneticist can apply the detailed physiological and medical knowledge of man to the interpretation of the effects of gene substitutions on each other's selective values, and human populations can provide data on an extreme case of an organism in which intra- and interpopulation interactions are especially pronounced. On the other hand, the current views of population structure and homeostasis will become important concepts in analyzing human populations. The study of this volume will be profitable to all who are interested in human genetics.

RICHARD LEVINS
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LETTERS TO THE EDITOR

March 5, 1957

To the Editor
Dear Sir:

Since you invite comment on the Report of the Committee on Genetic Effects of Atomic Radiation, may I call attention to a source of potential danger, as well as of invaluable genetic knowledge, in certain types of research conducted by human biologists? Ironically, some who should have been most aware of radiation hazards years ago—for these were known long before the Committee Report in June, 1956—have published descriptions of their X-ray procedures which constitute practices careless in the extreme. As an unintended result, long-term follow-up of persons so exposed, and whose exposure can be roughly estimated, can provide just that information on the genetic effects of radiation on man which is so urgently needed.

The research usually involves body tissue analysis or child growth. In some studies, roentgenograms have been taken of several unshielded body areas of infants and children, annually or every few months for a period of years, by untrained and unprotected assistants, usually young women, sometimes up to three in a room near the subject. In other studies, frequent films have been taken over several weeks or months, of certain body areas, some near the unprotected gonads, to investigate skeletal growth or changes in body fat with diet, exercise, or maturation.

In most such programs, damage to the exposed person is of course less likely than to his germ plasm. While the technical assistant, repeatedly exposed, may eventually develop somatic radiation damage, an individual subject is less likely to, but the increased sensitivity of the young and of growing tissues should be noted. A conscientious investigator may measure dosage received (all should, but few do!) and, if it is "safe" by current standards, may conclude that all is well. This is far from the case, as the Committee Report emphasizes.

Let us hope that such practices have changed since June, 1956, and that all investigators now feel obliged to justify their use of radiation, to shield the gonads, and to specify—to colleagues, subjects, and subjects' parents—the safeguards taken and dosages received.

The human biologist, though perhaps no more culpable in this regard than the physician or dentist, is more vulnerable, since his research often involves repeated exposures of individuals during early life and is obviously not for the patient's health. His profession has no formalized code of ethics or broad public support, he carries no malpractice insurance, and with X-rays he is handling a dangerous agent, in the use of which he is largely untrained. He should therefore think long and hard before using X-rays at all. One criterion might be whether he would permit his child to serve as subject or assistant in the program. Other informed parents may be less enthusiastic.

If X-rays are used, continuous monitoring of the procedure and consultation with a radiologist specifically interested in radiation hazard are minimal essentials. The human biologist who initiates and directs a study utilizing X-rays cannot delegate his responsibility to advisers, consultants, or even administrative superiors, whatever their degrees. Should damage result, he and his profession may be called to account. Indeed, by virtue of his knowledge of genetics, he should be able to restrain physicians and dentists in charge of research programs from excessive investigative zeal.

Human biologists are motivated personally as well as professionally by concern for human welfare. Those engaged in or contemplating X-ray studies should recognize their heavy responsibility to their assistants, their subjects, and their profession.

ALBERT DAMON
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April 17, 1957

Addendum: In discussing the substance of the above letter, several eminent authorities, including Professors of Anthropology, Medicine, and Radiology from four universities, agreed with its philosophy and mentioned some further relevant points. To list them: While one cannot be sure of the

degree of genetic damage caused by radiation in man, present evidence strongly suggests that we should err on the side of caution. Leading medical and dental journals have taken editorial note of radiation hazard. Radiologists, in attempting to minimize diagnostic exposure, even question time-honored procedures like the annual chest film of adolescents, or the comparison of normal with damaged limbs or joints. Shielding of gonads does not eliminate all hazard, since scatter and secondary radiation inside the body can reach the gonads. It will be a long time before newer devices for reducing exposure become widespread, and exposure may actually be increased while their use is being learned.

One renowned pediatric radiologist doubted the advisability of radiating, by X-rays or isotopes, any normal child for research purposes, whereas others believed that the value of the data to be obtained should be weighed against the danger. Included in such assessment should be reliability tests on measurements of X-ray films, especially on infants and children, who are notoriously difficult to pose.

Apart from biology and ethics, and in view of the increasing public awareness of radiation hazard, it was believed wise from the legal standpoint to conduct any research involving radiation with the greatest circumspection.

ALBERT DAMON

June 5, 1957

To the Editor
Dear Sir:

I shall never try to equal the volume of over 300 letters which Dr. Dight wrote to various editors. However, having indulged in a solicited communication which appeared in the December 1956 issue of the American Journal of Human Genetics, I am impelled to add an unsolicited sequel.

In my previous letter it was assumed that my family had been searched by fluoroscope upon our return from Europe. My assumption was based upon my observation of a box-like apparatus behind which was an operator who searched us. Later I learned from a nationally known radiologist that a modified fluoroscope had been constructed in San Francisco for the Bureau of Customs.

After my letter was written I eventually got around to making an enquiry at the Bureau of Customs and received the following reply, in part: "The electronic instruments described in your letter are classified under the provisions of Executive Order 10501 as information in the interest of national defense. However, you are advised that neither of the two instruments used by customs officers in the examination of your baggage and effects operates on the fluoroscope principle. You may be assured that the instruments will in no way affect the genetic composition of individuals. Very truly yours, Ralph Kelly, Commissioner of Customs."

From this reply one would conclude that the instruments receive but do not transmit radiations and therefore are not mutagenic.

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